AM

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 31/325

A1

(11) International Publication Number: WO 97/18805

(43) International Publication Date: 29 May 1997 (29.05.97)

(21) International Application Number: PCT/US96/18124

(22) International Filing Date: 12 November 1996 (12.11.96)

(30) Priority Data:
08/561,594 21 November 1995 (21.11.95) US

(60) Parent Application or Grant
(63) Related by Continuation
US 08/561,594 (CIP)
Filed on 21 November 1995 (21.11.95)

(71) Applicant *(for all designated States except US)*: MEDINOX, INC. [US/US]; Suite E, 11555 Sorrento Valley Road, San Diego, CA 92121 (US).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: LAI, Ching-San [US/US]; 209 Lolita Street, Encinitas, CA 92024 (US).

(74) Agent: REITER, Stephen; Pretty, Schroeder, Brueggemann & Clark, Suite 2000, 444 South Flower Street, Los Angeles, CA 90071 (US).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: COMBINATIONAL THERAPEUTIC METHODS EMPLOYING NITRIC OXIDE SCAVENGERS

(57) Abstract

In accordance with the present invention, there are provided combinational therapeutic methods for the *in vivo* inactivation or inhibition of formation (either directly or indirectly) of species which induce the expression of nitric oxide synthase, as well as reducing nitric oxide levels produced as a result of .No synthase expression. In contrast to the inhibitory approach described in the prior art (i.e., wherein the function of the enzymes responsible for nitric oxide production is inhibited), the present invention employs a combination of inactivation (or inhibition) and scavenging approach whereby the stimulus of nitric oxide synthase expression is inactivated, or the production thereof is inhibited, and overproduced nitric oxide is bound *in vivo* to a suitable nitric oxide scavenger. The resulting complexes render the stimulus of nitric oxide synthase expression inactive (or inhibit the production thereof), and nitric oxide harmless. The resulting complexes are eventually excreted in the urine of the host. Further in accordance with the present invention, there are provided compositions and formulations useful for carrying out the above-described methods.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia	**GB**	United Kingdom	**MW**	Malawi
AT	Austria	**GE**	Georgia	**MX**	Mexico
AU	Australia	**GN**	Guinea	**NE**	Niger
BB	Barbados	**GR**	Greece	**NL**	Netherlands
BE	Belgium	**HU**	Hungary	**NO**	Norway
BF	Burkina Faso	**IE**	Ireland	**NZ**	New Zealand
BG	Bulgaria	**IT**	Italy	**PL**	Poland
BJ	Benin	**JP**	Japan	**PT**	Portugal
BR	Brazil	**KE**	Kenya	**RO**	Romania
BY	Belarus	**KG**	Kyrgystan	**RU**	Russian Federation
CA	Canada	**KP**	Democratic People's Republic of Korea	**SD**	Sudan
CF	Central African Republic			**SE**	Sweden
CG	Congo	**KR**	Republic of Korea	**SG**	Singapore
CH	Switzerland	**KZ**	Kazakhstan	**SI**	Slovenia
CI	Côte d'Ivoire	**LI**	Liechtenstein	**SK**	Slovakia
CM	Cameroon	**LK**	Sri Lanka	**SN**	Senegal
CN	China	**LR**	Liberia	**SZ**	Swaziland
CS	Czechoslovakia	**LT**	Lithuania	**TD**	Chad
CZ	Czech Republic	**LU**	Luxembourg	**TG**	Togo
DE	Germany	**LV**	Latvia	**TJ**	Tajikistan
DK	Denmark	**MC**	Monaco	**TT**	Trinidad and Tobago
EE	Estonia	**MD**	Republic of Moldova	**UA**	Ukraine
ES	Spain	**MG**	Madagascar	**UG**	Uganda
FI	Finland	**ML**	Mali	**US**	United States of America
FR	France	**MN**	Mongolia	**UZ**	Uzbekistan
GA	Gabon	**MR**	Mauritania	**VN**	Viet Nam

COMBINATIONAL THERAPEUTIC METHODS EMPLOYING NITRIC OXIDE SCAVENGERS

FIELD OF THE INVENTION

The present invention relates to methods for directly or indirectly treating the production of species which induce the expression of nitric oxide synthase in mammals. In a particular aspect, the present invention relates to methods for inactivating such species, or inhibiting the production of such species, while, at the same time, reducing nitric oxide levels, by co-administration of agents which inactivate (or inhibit the production of) such species, along with a scavenger of overproduced nitric oxide. In a further aspect, the present invention relates to compositions and formulations useful in the methods disclosed herein.

BACKGROUND OF THE INVENTION

In 1987, nitric oxide (·NO), a gaseous free-radical, was discovered in humans (see, for example, Ignarro et al., in *Proc. Natl. Acad. Sci., USA* **84**:9265-69 (1987) and Palmer et al., in *Nature* **327**:524-26 (1987)). As an indication of the significance of this discovery for the understanding of human physiology and pathophysiology, Science magazine selected nitric oxide as the molecule of the year in 1992.

Nitric oxide is formed from the terminal guanidino nitrogen atom of L-arginine by nitric oxide synthase (NOS; see, for example, Rodeberg et al., in *Am. J. Surg.* **170**:292-303 (1995), and Bredt and Snyder in *Ann. Rev. Biochem.* **63**:175-95 (1994)). Two major forms of nitric oxide synthase, constitutive and inducible enzymes, have been identified.

Under physiological conditions, a low output of ·NO is produced by the constitutive, calcium-dependent NOS isoform (cNOS) present in numerous cells, including endothelium and neurons. This low level of nitric oxide is involved in a variety of regulatory processes, e.g., blood vessel homeostasis, neuronal communication and immune system function. On the other hand, under pathophysiological conditions, a high output of ·NO is produced by the inducible, calcium-independent NOS isoform (iNOS) which is expressed in numerous cell types, including endothelial cells, smooth muscle cells and macrophages. These high levels of nitric oxide have been shown to be the etiology of endotoxin shock. This high output of ·NO further contributes to inflammation-related tissue damage, neuronal pathology, N-nitrosamine-induced carcinogenesis and mutations in human cells and bacteria via deamination reaction with DNA. Nitric oxide can therefore be seen to be a mixed blessing, being very desirable when present in small amounts, while potentially being highly detrimental when produced in excessive quantities.

Nitric oxide is a potent vasodilator (see, for example, Palmer in *Arch. Surg.* **128**:396-401 (1993) and Radomski & Moncada in *Thromb. Haemos.* **70**:36-41 (1993). For example, in blood, ·NO produced by the endothelium diffuses isotropically in all directions into adjacent tissues. As ·NO diffuses into the vascular smooth muscle, it binds to guanylate cyclase enzyme, which catalyzes the production of cGMP, inducing vasodilation (see, for example, Ignarro, L.J., *Ann. Rev. Toxicol.* **30**:535-560 (1990); Moncada, S., *Acta Physiol. Scand.* **145**:201-227 (1992); and Lowenstein and Snyder, *Cell* **70**:705-707 (1992)). The overproduction of nitric oxide causes an extreme drop in blood pressure, resulting in insufficient tissue perfusion and organ failure, syndromes that are associated with many diseases and/or conditions (e.g., septic shock, overexpression of cytokines, allograft rejection, and the like). The

overproduction of nitric oxide is triggered by a number of stimuli, such as, the overproduction of inflammatory cytokines (e.g., tumor necrosis factor (TNF), interleukin-1 (IL-1), interferons, endotoxin, and the like). Additionally, the overproduction of ·NO has been discovered to be one of the major side-effects of cytokine therapy (see, for example, Miles et al., in *Eur. J. Clin. Invest.* **24**:287-290 (1994) and Hibbs et al., in *J. Clin. Invest.* **89**:867-877 (1992)). Thus, abnormally elevated nitric oxide levels have been linked to many inflammatory and infectious diseases.

Inflammatory cytokines (e.g., TNF, interleukins or interferons) and infectious agents (e.g., endotoxin) induce nitric oxide overproduction by inducing transcription of the inducible nitric oxide synthase gene, leading to the production of inducible nitric oxide synthase, which in turn results in the overproduction of nitric oxide. The production of nitric oxide by the above-described pathway can be disrupted in a variety of ways. Thus, for example, there have been attempts to develop monoclonal antibodies (e.g., anti-endotoxin antibodies, anti-cytokine antibodies, anti-cytokine receptor antibodies, and the like) in efforts to block the ·NO production pathway at the transcriptional level. Unfortunately, however, such efforts have met with very limited success (see, for example, Glauser et al., in *Clin. Infect. Dis.* **18**:S205-16 (1994) and St. John & Dorinsky, in *Chest* **103**:932-943 (1993)). At least one reason for the relative lack of success in the art is the fact that the production of inflammatory cytokines is short-lived (see, for example, Wange & Steinsham in *Eur. J. Haematol.* **50**:243-249 (1993)), while overproduction of nitric oxide lasts several days, causing systemic hypotension, insufficient tissue perfusion and organ failure.

Thus, for example, during endotoxemia, TNF production peaks at about 1-2 hours. Therefore, in order to be effective, anti-TNF antibodies would have to be administered at an early stage after infection. Indeed, in many clinical settings, patients are likely to already have been infected with bacteria prior to being admitted. Accordingly, such therapeutic methods have met with only limited success.

Currently, many pharmaceutical companies have turned their attention to the design and development of substrate or product analogue inhibitors of the enzyme, NOS, in efforts to treat the overproduction of ·NO. However, recent data show that the inhibition of NOS is detrimental to subjects. For example, rodent studies show that inhibition of the production of nitric oxide causes intrauterine growth retardation and hind-limb disruptions in rats (see, for example, Diket et al., in *Am. J. Obstet. Gynecol.* **171**:1243-1250 (1994)). Furthermore, the inhibition of nitric oxide synthesis during endotoxemia has also been shown to be detrimental (see, for example, Minnard et al., in *Arch. Surg.* **129**:142-148 (1994); Luss et al., in *Biochem. Biophys. Res. Commun.* **204**:635-640 (1994); and Hargrecht et al., in *J. Leuk. Biol.* **52**:390-394 (1992)). Similar results have been reported in larger animal studies, such as dogs and swine (see, for example, Statman et al., in *J. Surg. Res.* **57**:93-98 (1994); Mitaka et al., *Am. J. Physiol.* **268**:H2017-H2023 (1994); Robertson, et al., *Arch. Surg.* **129**:149-156 (1994); and Henderson et al., *Arch. Surg.* **129**:1271-1275 (1994)).

Since a variety of stimuli induce expression of nitric oxide synthase, which, in turn, leads to nitric oxide overproduction (with its attendant detrimental effects), there is a need in the art to effectively treat both the initial stimulus of nitric oxide synthase

expression, and the resulting overproduction of nitric oxide.

BRIEF DESCRIPTION OF THE INVENTION

In accordance with the present invention, combinational therapeutic methods have been developed for the *in vivo* inactivation or inhibition of formation (either directly or indirectly) of species which induce the expression of inducible nitric oxide synthase, as well as reducing nitric oxide levels produced as a result of ·NO synthase expression. In contrast to the inhibitory approach described in the prior art to address the problem of nitric oxide overproduction (see, for example, Aisaka et al., *Biochem. Biophys. Res. Commun.* **60**:881-886 (1989); Rees, et al., *Proc. Natl. Acad. Sci. USA* **86**:3375-3379, (1989)); Henderson et al., in *Arch. Surg.* **129**:1271-1275 (1994); Hambrecht et al., in *J. Leuk. Biol.* **52**:390-394 (1992); Luss et al., in *Biochem. and Biophys. Res. Comm.* **204**:635-640 (1994); Robertson et al., in *Arch. Surg.* **129**:149-156 (1994); Statman et al., in *J. Surg. Res.* **57**:93-98 (1994); and Minnard et al., in *Arch. Surg.* **129**:142-148 (1994)), the present invention employs a combination of inactivation (and/or inhibition) and scavenging approach whereby the stimulus of nitric oxide synthase expression is inactivated and/or expression thereof is inhibited, and overproduced nitric oxide is bound *in vivo* to a suitable nitric oxide scavenger. The resulting complexes render the stimulus of nitric oxide synthase expression inactive (or inhibit the production thereof), while also rendering the resulting nitric oxide harmless. The resulting complexes are eventually excreted in the urine of the host. Further in accordance with the present invention, there have been developed compositions and formulations useful for carrying out the above-described methods.

Numerous stimuli for ·NO synthase are known in the art. Co-administration of agents which inactivate the stimulus of ·NO synthase expression (or inhibit the production thereof), in combination with nitric oxide scavengers as described herein, provides a more effective means to treat a variety of indications than has previously been described in the art.

An exemplary nitric oxide scavenger contemplated for use in the practice of the present invention is a dithiocarbamate-ferrous iron complex. This complex binds to ·NO, forming a stable, water-soluble dithiocarbamate-iron-NO complex having a characteristic three-line spectrum (indicative of a mononitrosyl-Fe complex) which can readily be detected at ambient temperatures by electron paramagnetic resonance (EPR) spectroscopy (See Komarov et al., in *Biochem. Biophys. Res. Commun.* **195**:1191-1198 (1993); and Lai and Komarov, *FEBS Lett.*,**345**:120-124, (1994)). This method of detecting ·NO in body fluids in real time has recently been described by Lai in U.S. Patent No. 5,358,703, incorporated by reference herein in its entirety.

The present invention relates to combinational therapeutic methods for treating the production of species which induce the expression of nitric oxide synthase in mammals. Thus, a dual attack is mounted against a variety of stimuli which lead to the production of dangerously high *in vivo* levels of ·NO. Combinations of agents contemplated for use in the practice of the present invention (i.e., agents capable of inactivating species which induce expression of inducible nitric oxide, or agents which inhibit the production of such species, and nitric oxide scavengers) are administered to a host in need of such treatment. The agent capable of inactivating (or inhibiting the production of) species which induce expression of inducible nitric oxide and ·NO scavengers

interact with the stimulus of nitric oxide synthase expression and *in vivo* produced ·NO, respectively, forming a complex between said species and said agent, as well as a stable scavenger-NO complex. Whereas free ·NO is a potent vasodilator, chelated ·NO complexes are not. The NO-containing complex is then filtered through the kidneys, concentrated in the urine, and eventually excreted by the subject, thereby reducing *in vivo* ·NO levels.

BRIEF DESCRIPTION OF THE FIGURE

Figure 1 illustrates the effects of endotoxin (LPS-4 mg/kg) treatment on mean arterial pressure (MAP) with and without [$(MGD)_2$/Fe] treatment. Bolus i.v. injection of LPS at time zero was as indicated in the Figure. Data marked by open circles [○] are the result of bolus i.v. injection of 1.0 ml saline, followed by 1.0 ml/hr of continuous saline infusion (n=11/16, note: 11 out of 16 animals died before the end of the experiments). Data marked by closed circles [●], are the result of [$(MGD)_2$/Fe] infusion, 0.1 mmole/kg loading dose followed by 0.1 mmole/kg/hr i.v. infusion (n=3/16, note: only 3 out of 16 animals died before the end of the experiments). Data points marked with an asterisk (*) indicate the results are significantly different at $p < 0.05$. The ratio of MGD to Fe used was 5:1 (MGD:Fe), and the dosage shown was with respect to MGD.

DETAILED DESCRIPTION OF THE INVENTION

In accordance with the present invention, there are provided combinational therapeutic methods for directly or indirectly treating the production of species which induce the expression of inducible nitric oxide synthase in a subject. Invention methods comprise:

co-administering to a subject an effective amount of a combination of at least one agent

capable of directly or indirectly inactivating said species, or inhibiting production of said species, and at least one nitric oxide scavenger.

As readily recognized by those of skill in the art, a variety of agents can be used to scavenge nitric oxide. Examples of suitable agents for this purpose include non-heme iron-containing peptides or proteins, porphyrins, metalloporphyrins, dithiocarbamates, dimercaptosuccinic acid, phenanthroline, desferrioxamine, pyridoxal isonicotinoyl hydrazone (PIH), 1,2-dimethyl-3-hydroxypyrid-4-one (L1), [+] 1,2-bis(3,5-dioxopiperazine-1-yl)propane (ICRF-187), and the like. A presently preferred class of compounds useful for such purpose is the dithiocarbamates. Dithiocarbamate-containing nitric oxide scavengers contemplated for use in the practice of the present invention include any physiologically compatible derivative of the dithiocarbamate moiety (i.e., $(R)_2N-C(S)-SH$). Such compounds can be described with reference to the following generic structure (I):

$$[R_1R_2N-C(S)-S^-]_x\ M^{+1,\ +2,\ +3} \qquad (I)$$

wherein:

each R_1 and R_2 is independently selected from a C_1 up to C_{18} alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocyclic, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, alkylaryl, substituted alkylaryl, arylalkyl, substituted arylalkyl, arylalkenyl, substituted arylalkenyl, arylalkynyl, substituted arylalkynyl, aroyl, substituted aroyl, acyl, substituted acyl or R_1 and R_2

can cooperate to form a 5-, 6- or 7-membered ring including N, R_1 and R_2,

x is 1 or 2, and

M is a monovalent cation when x is 1, or M is a physiologically compatible divalent or trivalent transition metal cation when x is 2.

Presently preferred compounds having the above-described generic structure (I) are those wherein:

each of R_1 and R_2 = a C_1 up to C_{12} alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl or substituted alkynyl, wherein the substituents are selected from carboxyl, -C(O)H, oxyacyl, phenol, phenoxy, pyridinyl, pyrrolidinyl, amino, amido, hydroxy, nitro or sulfuryl, and

M = Fe^{+2} or Fe^{+3}.

Especially preferred compounds having the above-described generic structure are those wherein:

R_1 = a C_2 up to C_8 alkyl or substituted alkyl, wherein the substituents are selected from carboxyl, acetyl, pyridinyl, pyrrolidinyl, amino, amido, hydroxy or nitro,

R_2 is selected from a C_1 up to C_6 alkyl or substituted alkyl, or R_2 can cooperate with R_1 to form a 5-, 6- or 7-membered ring including N, R_2 and R_1, and

M = Fe^{+2}.

The presently most preferred compounds having the above-described generic structure are those wherein:

R_1 = a C_2 up to C_8 alkyl or substituted alkyl, wherein the substituents are

selected from carboxyl, acetyl, amido or hydroxy,

R_2 = a C_1 up to C_4 alkyl or substituted alkyl, and

M = Fe^{+2}.

When R_1 and R_2 cooperate to form a 5-, 6- or 7-membered ring, the combination of R_1 and R_2 can be a variety of saturated or unsaturated 4, 5 or 6 atom bridging species selected from alkenylene or -O-, -S-,-C(O)- and/or -N(R)-containing alkylene moieties, wherein R is hydrogen or a lower alkyl moiety.

Monovalent cations contemplated for incorporation into compounds of structure (I) include H^+, Na^+, NH_4^+, tetraalkyl ammonium, and the like. Physiologically compatible divalent or trivalent transition metal cations contemplated for incorporation into the above compounds include charged forms of iron, cobalt, copper, manganese, or the like (e.g., Fe^{+2}, Fe^{+3}, Co^{+2}, Co^{+3}, Cu^{+2}, Mn^{+2} or Mn^{+3}). In accordance with the present invention, the ratio of dithiocarbamate-species to counter-ion M can vary widely. Thus, dithiocarbamate-containing nitric oxide scavenger can be administered without any added metallic counter-ion (i.e., M = H^+, or a transition metal cation to dithiocarbamate-species ratio of zero), with ratios of transition metal cation to dithiocarbamate-species up to about 1:2 (i.e., a 2:1 dithiocarbamate:transition metal cation complex) being suitable.

As employed herein, "substituted alkyl" comprises alkyl groups further bearing one or more substituents selected from hydroxy, alkoxy (of a lower alkyl group; wherein a lower alkyl group has about 1-4 carbon atoms), mercapto (of a lower alkyl group), cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl,

aryloxy, substituted aryloxy, halogen, trifluoromethyl, cyano, nitro, nitrone, amino, amido, -C(O)H, acyl, oxyacyl, carboxyl, carbamate, sulfonyl, sulfonamide, sulfuryl, and the like.

As employed herein, "cycloalkyl" refers to cyclic ring-containing groups containing in the range of about 3 up to 8 carbon atoms, and "substituted cycloalkyl" refers to cycloalkyl groups further bearing one or more substituents as set forth above.

As employed herein, "alkenyl" refers to straight or branched chain hydrocarbyl groups having at least one carbon-carbon double bond, and having in the range of about 2 up to 12 carbon atoms, and "substituted alkenyl" refers to alkenyl groups further bearing one or more substituents as set forth above.

As employed herein, "alkynyl" refers to straight or branched chain hydrocarbyl groups having at least one carbon-carbon triple bond, and having in the range of about 2 up to 12 carbon atoms, and "substituted alkynyl" refers to alkynyl groups further bearing one or more substituents as set forth above.

As employed herein, "aryl" refers to aromatic groups having in the range of 6 up to 14 carbon atoms and "substituted aryl" refers to aryl groups further bearing one or more substituents as set forth above.

As employed herein, "alkylaryl" refers to alkyl-substituted aryl groups and "substituted alkylaryl" refers to alkylaryl groups further bearing one or more substituents as set forth above.

As employed herein, "arylalkyl" refers to aryl-substituted alkyl groups and "substituted arylalkyl" refers

to arylalkyl groups further bearing one or more substituents as s t forth above.

As employed herein, "arylalkenyl" refers to aryl-substituted alkenyl groups and "substituted arylalkenyl" refers to arylalkenyl groups further bearing one or more substituents as set forth above.

As employed herein, "arylalkynyl" refers to aryl-substituted alkynyl groups and "substituted arylalkynyl" refers to arylalkynyl groups further bearing one or more substituents as set forth above.

As employed herein, "aroyl" refers to aryl-carbonyl species such as benzoyl and "substituted aroyl" refers to aroyl groups further bearing one or more substituents as set forth above.

As employed herein, "heterocyclic" refers to cyclic (i.e., ring-containing) groups containing one or more heteroatoms (e.g., N, O, S, or the like) as part of the ring structure, and having in the range of 3 up to 14 carbon atoms and "substituted heterocyclic" refers to heterocyclic groups further bearing one or more substituents as set forth above.

As employed herein, "acyl" refers to alkyl-carbonyl species.

As employed herein, "halogen" refers to fluoride, chloride, bromide or iodide atoms.

Induction of expression of inducible nitric oxide synthase, and hence, overproduction of nitric oxide, is associated with a wide range of disease states and/or indications, such as, for example, septic shock, hemorrhagic shock, anaphylactic shock, toxic shock

syndrome, ischemia, cerebral ischemia, administration of cytokines, overexpression of cytokines, ulcers, inflammatory bowel disease (e.g., ulcerative colitis or Crohn's disease), diabetes, arthritis, asthma, Alzheimer's disease, Parkinson's disease, multiple sclerosis, cirrhosis, allograft rejection, encephalomyelitis, meningitis, pancreatitis, peritonitis, vasculitis, lymphocytic choriomeningitis, glomerulonephritis, uveitis, ileitis, inflammation (e.g., liver inflammation, renal inflammation, and the like), burn, infection (including bacterial, viral, fungal and parasitic infections), hemodialysis, chronic fatigue syndrome, stroke, cancers (e.g., breast, melanoma, carcinoma, and the like), cardiopulmonary bypass, ischemic/reperfusion injury, gastritis, adult respiratory distress syndrome, cachexia, myocarditis, autoimmune disorders, eczema, psoriasis, heart failure, heart disease, atherosclerosis, dermatitis, urticaria, systemic lupus erythematosis, AIDS, AIDS dementia, chronic neurodegenerative disease, chronic pain, priapism, cystic fibrosis, amyotrophic lateral sclerosis, schizophrenia, depression, premenstrual syndrome, anxiety, addiction, migraine, Huntington's disease, epilepsy, neurodegenerative disorders, gastrointestinal motility disorders, obesity, hyperphagia, solid tumors (e.g., neuroblastoma), malaria, hematologic cancers, myelofibrosis, lung injury, graft-versus-host disease, head injury, CNS trauma, hepatitis, renal failure, liver disease (e.g., chronic hepatitis C), drug-induced lung injury (e.g., paraquat), myasthenia gravis (MG), ophthalmic diseases, and the like.

Treatment of such conditions can be carried out with such reagents as anti-cytokine antibodies, anti-cytokine receptor antibodies, anti-endotoxin antibodies, bradykinin antagonists, synthetic peptide blocking bradykinin receptors, bactericidal/permeability increasing protein, antibodies to platelet activating factor, and the

like. Such agents can be used for a variety of indications, such as for example, anti-endotoxin therapy (e.g., antibodies to endotoxin, antibodies to LPS-binding protein, soluble CD14 protein, bactericidal/permeability increasing protein, polymyxin B, and the like), inhibition of cytokine synthesis/release (e.g., employing phosphodiesterase inhibitors, IL-4, IL-10, IL-13, TGF-ß, corticosteroids, and the like), anti-cytokine therapy (e.g., employing antibodies to TNF, soluble TNF receptors, IL-1 receptor antagonists, antibodies to IL-1 receptors, antibodies to IL-6, antibodies to interferon-γ, soluble interferon-γ receptors, and the like), inhibition of the coagulation cascade (and of complement activation, employing such agents as anti-Factor XII antibodies, antibodies to C5a, C1-esterase inhibitors, soluble Cr1, and the like), inhibition of platelet activating factor (PAF, employing such agents as PAF receptor antagonists), inhibition of arachidonate metabolism (e.g., employing agents such as cyclooxygenase inhibitors, lipoxygenase inhibitors, leukotriene inhibitors, thromboxane A_2 inhibitors, prostaglandins, and the like), inhibition of nitric oxide synthase enzymes (e.g., employing N-methyl-L-arginine, ϵ-N-iminoethyl-L-lysine, aminoguanidine, S-methyl isothiourea sulfate, and the like), immunosuppression (e.g., employing agents such as cyclosporin A, OKT3, FK506, and the like), diabetic therapy (e.g., employing agents such as free pancreatic islets, encapsulated pancreatic islets, oral insulin, intravenous insulin, amylin hormone, and the like), dihydropyridine calcium channel blockers (e.g., employing agents such as nifedipine, nitrendipine, nisoldipine, and the like), inflammatory disease therapy (e.g., employing agents such as sulfasalazine, mesalamine, corticosteroids, azathioprine, 6-mercaptopurine, metronidazole, aspirin, phenyl butyl nitrone (PBN), and the like), and so on.

In addition, administration of many therapeutic agents can also lead to the induction of expression of inducible nitric oxide synthase, and hence, overproduction of nitric oxide. For example, nitric oxide overproduction is also associated with the following treatments, such as, for example, administration of immunosuppressants, such as glucocorticoids (methylprednisolone), myelin basic protein (e.g., 7-capaxone), anti-Fc receptor monoclonal antibodies, hydroorotate dehydrogenase inhibitor, anti-IL2 monoclonal antibodies (e.g., CHI-621 and dacliximab), buspirone, castanospermine, CD-59 (complement factor inhibitor), 5-lipoxygenase inhibitor (e.g., CMI-392), phosphatidic acid synthesis antagonists, ebselen, edelfosine, enlimomab, galaptin, platelet activating factor antagonists, selectin antagonists (e.g., ICAM-4), interleukin-10 agonist, macrocylic lactone, methoxatone, mizoribine, OX-19, peptigen agents, PG-27, protein kinase C inhibitors, phosphodiesterase IV inhibitor, single chain antigen binding proteins, complement factor inhibitor, sialophorin, sirolimus, spirocyclic lactams, 5-hydroxytryptamine antagonist, anti-TCR monoclonal antibodies, CD5 gelonin, TOK-8801, and the like.

Additional treatments which lead to the overexpression of nitric oxide include administration of antimetabolite cytotoxics (e.g., azathioprine, cyclophosphamide), C5a release inhibitor, benzydamine, peldesine, pentostatin, SDZ-ASM-981, thalidomide, benzoporphyrin derivatives, arachidonate antagonists (e.g., halometasone, halobetasol propionate), corticosteriod (clobetasol propionate), growth hormone antagonists (octapeptide somatostatin analogue, lanreotide, angiopeptin and dermopeptin), thymopentin, and the like.

Other treatments which lead to the overexpression of nitric oxide include administration of neuroprotective agents, such as α-adrenoreceptor antagonist (e.g.,

α-dihydroergocryptine), NMDA antagonists (e.g., 5,6,7-tichloro-THQTQ, remacemide, 2-piperazinecarboxylic acid, N-indologlycinamide derivatives, spiro[benzo(b)thiophen-4(5H)] derivatives, CP-101606, eliprodil, dexanabinol, GV-150526, L-695902, L-701324, amantadine derivatives, dizocilpine, benzomorphan derivatives, aptiganel, (S)-α-phenyl-2-pyridine ethanamide dihyrochloride, 1-amino-cyclopentanecarboxylic acid, and the like), sodium channel antagonists (e.g., 619C89), glycine antagonists (e.g., glystasins), calcium channel antagonists (e.g., 3,5-pyridinedicarboxylic acid derivatives, conopeptides, 1-piperazineethanol, thieno[2,3-b]pyridine-5-carboxylic acid derivatives, NS-3034, nilvadipine, nisoldipine, tirilazad mesylate, 2H-1-enzopyran-6-ol, nitrone spin traps, iacidipine, iomeerzine hydrochloride, lemildipine, lifarizine, CPC-304, efonidipine, F-0401, piperazine derivatives, and the like), calpain inhibitors, fibrinogen antagonists (e.g., ancrod), integrin antagonists (e.g., antegren), thromboxane A_2 antagonist (e.g., 9H-carbazole-9-propanoic acid derivatives, 5-Heptenoic acid derivatives, 1-azulene-sulfonic acid derivatives, and the like), brain-derived neurotropic factor, adrenergic transmitter uptake inhibitor (e.g., 1-butanamine), endothelin A receptor antagonists (e.g., benzenesulfonamide derivatives), GABA A receptor antagonists (e.g., triazolopyrimidine derivatives, cyclohexaneacetic acid derivatives, and the like), GPIIb IIIa receptor antagonists (e.g., C68-22), platelet aggregation antagonist (e.g., 2(1H)-quinolinone derivatives, 1H-pyrrole-1-acetic acid derivatives, coumadin, and the like), Factor Xa inhibitor, CPC-211, corticotropin releasing factor agonist, thrombin inhibitor (e.g., cothrombins, fraxiparine, dermatan sulfate, heparinoid, and the like), dotarizine, intracellular calcium chelators (e.g., BAPTA derivatives), radical formation antagonists (e.g., EPC-K1, 3-pyridinecarboxamide derivatives, superoxide dismutase, raxofelast, lubeluzole,

3H-pyrazol-3-one derivatives, kynurenic acid derivatives, homopiperazine derivatives, polynitroxyl albumin, and the like), protein kinase inhibitors (e.g., 1H-1,4-diazepine), nerve growth agonist (e.g., floor plate factor-5), glutamate antagonist (e.g., cyclohexanepropanoic acid, riluzole, NS-409, acetamide derivatives, and the like), lipid peroxidase inhibitors (e.g., 2,5-cyclohexadiene-1,4-dione derivatives), sigma receptor agonist (e.g., cyclopropanemethanamine derivatives, SA-4503, and the like), thyrotropin releasing hormone agonist (e.g., JTP-2942, L-prolinamide, posatirelin, and the like), prolyl endopeptidase inhibitor, monosialoganglioside GM1, proteolytic enzyme inhibitor (e.g., nafamostat), neutrophil inhibitory factor, platelet activating factor antagonist (e.g., nupafant), monoamine oxidase B inhibitor (e.g., parafluoroselegiline, benzonitrile derivatives, and the like), PARS inhibitors, Angiotensin I converting enzyme inhibitor (e.g., perindopril, ramipril, and the like), acetylcholine agonist (e.g., pramiracetam), protein systhesis antagonist (e.g., procysteine), phosphodiesterase inhibitor (e.g., propentofylline), opioid kappa receptor agonist (e.g., 10H-phenothiazine-2-carboxamine derivatives), complement factor inhibitor (e.g., sCRI fragments), somatomedin-1, carnitine acetyltransferase stimulant (e.g., acetylcarnitine), and the like.

Still further treatments which lead to the overproduction of nitric oxide include administration of T cell inhibitors, such as synthetic leucocyte antigen derived peptides, interleukin-1 receptor antagonist, MG/AnergiX, anti-CD3 monoclonal antibodies, anti-CD23 monoclonal antibodies, anti-CD28 antibodies, anti-CD2 monoclonal antibodies, CD4 antagonists, anti-E selectin antibodies, MHC inhibitors, monogens, mycophenolate mofetil, and the like.

Additional treatments which lead to overproduction of nitric oxide include administration of antimigraine agents, such as MK-462, 324C91, Phytomedicine, (S)-fluoxetine, calcium channel antagonists (e.g., nimodipine/Nimotop, flunarizine, dotarizine/FI-6026, iomerizine HCL/KB-2796, CPC-304, CPC-317, and the like), α-dihydroergocryptine, 5-HT1 agonists, (e.g., Sumatriptan/Imitrex, Imigran, GR-85548, 311C, GR-127607, and the like), 5-HT1D agonists, 5-HT1A antagonists, 5-HT1B antagonists (e.g., CP-93129), 5-HT1D antagonists (e.g., 1H-indole-5-ethanesulfonamide derivatives, 1H-indole-5-methanesulfonamide, and the like), 5-HT1D receptor cloned (e.g., 5-HT1D agents), 2-thiophenecarboxamide, 3-piperidinamine, diclofenac potassium, dihydroergotamine (e.g., DHE 45®), dolasetron mesilate, dotarizine, flupirtine, histamine-H3 receptor agonist, indobufen, 1-azulenesulfonic acid derivatives, cholinesterase inhibitors, (e.g., S-9977), bradykinin antagonists, nitric oxide reductase inhibitors (e.g., BN-52296), nitric oxide receptor antagonists, substance P antagonists (e.g., Capsaicin/Nasocap), endopeptidase inhibitors (e.g., neutral endopeptidase, cloned), piperazine derivatives, neurokinin 1 antagonists, metergoline, dopamine D2 antagonist (e.g., metoclopramide + lysine acetyl), enkephalinase inhibitors (e.g., neutral endopeptidase), 5-HT2 antagonists (e.g., LY-053857), 5-HT3 antagonists (e.g., Dolasetron mesilate/MDL-73147, 4H-carbazol-4-one derivatives, and the like), tenosal, tolfenamic acid, cyclooxygenase inhibitors (e.g., carbasalate/carbaspirin calcium, tenosal/MR-Y134, and the like), alpha adrenoreceptor antagonists (e.g., arotinolol, dihydroergocryptine, and the like), opioid agonists (e.g., flupirtine/D-9998), beta adrenergic antagonists (e.g., propranolol), valproate semisodium, and the like.

Additional treatments which lead to the overproduction of nitric oxide include administration of

antiarthritic agents, such as anti-CD4 monoclonal antibodies, phospholipase A1 inhibitor, loteprednol, tobramycin, combination of loteprednol and tobramycin, salnacedin, amiprilose, anakinra, anergiX, anti-B7 antibody, anti-CD3H, anti-gp39, anti-MHC MAbs, antirheumatic peptides, anti-Tac(Fv)-PE40, AP-1 inhibitors, AR-324, purine nucleotide phosphorylase inhibitors (e.g., BCX-5), bindarit, CD2 antagonist (e.g., BTI-322), campath-1H, CD4 antagonist (e.g., CE9.1, SB-210396, and the like), tumor necrosis factor antagonist (e.g., p80 TNFR, rhTNFbp, peptide T, CenTNF, thalidomide, CDP-571, TBP-1, and the like), cobra venom factor, interleukin 1a agonist (e.g., cytogenin), interleukin 2 receptor antagonist (e.g., daclximab), ICAM 1 antagonist (e.g., enlimomab), interleukin 1 beta converting enzyme inhibitors (e.g., ICE-inhibitors), interferons (e.g., thymocartin), interleukin-10, interleukin-13, interleukin 1 antagonist (e.g., SR-31747, TJ-114, and the like), interleukin-2 antagonist (e.g., sirolimus), phospholipase C inhibitor, neurokinin 1 antagonist (e.g., L-733060), laflunimus, leflunomide, leucotriene antagonists, levamisole, LFA3TIP, macrocyclic lactone, MHC class II inhibitors, mizoribine, mycophenolate mofetil, NfkB inhibitors, oncolysin CD6, peldesine, pidotimod, PKC-RACK inhibitors, PNP inhibitors, reumacon, CD28 antagonist, roquinimex, RWJ-50271, subreum, T7 vector, tacrolimus, VLA antagonist (e.g., TBC-772), transforming growth factor beta agonist, methionine synthase inhibitors (e.g., vitamin B12 antagonist), adenosine A2 receptor agonist (e.g., YT-146), CD5 antagonist (e.g., zolimomab), 5-lipoxygenase inhibitor (e.g., zileuton, tenidap, ABT-761, and the like), cyclooxygenase inhibitor (e.g., tenoxicam, talmetacin, piroxicam cinnamate, oxaprozin, NXTHIO, ML-3000, mofezolac, nabumetone, flurbiprofen, aceclofenac, diclofenac, dexibuprofen, and the like), metalloproteinase inhibitor (e.g., XR-168, TNF convertase inhibitors, GI-155704A, AG-3340, BB-2983, and the like), nitric oxide synthase inhbitors (e.g., ARL-16556), phospholipase A2

inhibitor (e.g., ARL-67974), selectin antagonist (e.g., CAM inhibitors), leucotriene B4 antagonist (e.g., CGS-25019C), collagenase inhibitor (e.g., GR-129574A), cyclooxygenase 2 inhibitor (e.g., meloxicam), thromboxane synthase inhibitor (e.g., curcumin), cysteine protease inhibitor (e.g., GR-373), metalloproteinase inhibitor (D-5410), lipocortins synthesis agonist (e.g., rimexolone, predonisolone 21-farnesylate, HYC-141, deflazacort, and the like), chelating agent (e.g., diacerein), elastase inhibitors, DNA directed RNA polymerase inhibitor (e.g., estrogens), oxygen radical formation antagonist (e.g., glucosamine sulfate), thrombin inhibitors (e.g., GS-522), collagen inhibitors (e.g., halofuguinone), hyaluronic acid agonist (e.g., NRD-101, hylan, Dispasan, Hyalart, and the like), nitric oxide antagonists (e.g., hydroxocobalamin), stromelysin inhibitors (e.g., L-758354), prostaglandin E1 agonist (e.g., misoprostol, misoprostol+diclofenac, and the like), dihydrofolate reductase inhibitor (e.g., trimetrexate, MX-68, and the like), opioid antagonist (e.g., nalmefene), corticotropin releasing factor antagonist (e.g., NBI-103, NBI-104, and the like), proteolytic enzyme inhibitor (e.g., protease nexin-1, NCY-2010, and the like), bradykinin antagonist (e.g., tachykinin antagonists, NPC-17731, and the like), growth hormone antagonist (e.g., octreotide), phosphodiesterase IV inhibitor (e.g., PDEIV inhibitors), gelatinase inhibitor (e.g., REGA-3G12), free radical scavengers (e.g., SIDR-1026), prostaglandin synthase inhibitors (e.g., sulfasalazine), and the like.

Additional treatments which lead to the overproduction of nitric oxide include administration of agents useful for the treatment of septic shock, such as angiogenesis inhibitors (e.g., OLX-514), bradykinin antagonists (e.g., CP-0502, NPC-17731, and the like), complement factor inhibitors (e.g., C3 convertase inhibitor), C5a release inhibitors (.g., CAB-2.1), dopamine agonists (e.g., dopexamine), elastase inhibitors

(e.g., ONO-5046), E selectin antagonists (e.g., CY-1787), farnesyltransferase inhibitors (e.g., RBE limonene), immunostimulants (e.g., CGP-19835A, lipid A vaccine, edobacomab, nebacumab, StaphGAM, diabodies, and the like), immunosuppressants (e.g., CytoTAB, transcyclopentanyl purine analogues, and the like), interleukin 1 antagonists (e.g., interleukin 1 receptors), interleukin 1 receptor antagonists (e.g., anakinra), interleukin 1b antagonists (e.g., interleukin-1β), interleukin 1beta converting enzyme inhibitors (e.g., ICE-inhibitors), interleukin 8 antagonists (e.g., IL-8 receptor), interleukin 13 agonists (e.g., intereleukin-13), ITF-1697, lipase clearing factor inhibitors (e.g., SC-59735), membrane permeability enhancers (e.g., Bactericidal Permeability Increasing protein/BPI), nitric oxide antagonists (e.g., hydroxocobalamin), nitric oxide synthase inhibitors (e.g., L-NMMA, α-methyl-Ndelta-iminoethyl-ornithine, and the like), P2 receptor stimulants (e.g., ATP analogues), phosphatidic acid synthesis antagonists (e.g., lisofylline), phospholipase A2 inhibitors (e.g., S-448, acylpyrrole-alkanoic acid derivatives, indoleacetic acid derivatives, and the like), platelet activating factor antagonists (e.g., ABT-299, TCV-309, SM-12502, (2RS,4R)-3-(2-(3-pyridinyl)thiazolidin-4-oyl)indoles, UR-12670, E-5880, and the like), prostacyclin agonists (e.g., taprostene), prostaglandin E1 agonists (e.g., TLC C-53), protein kinase inhibitors (e.g., SB-203580), protein kinase C inhibitors, protein synthesis antagonists (e.g., procysteine), proteolytic enzyme inhibitors (e.g., nafamostat), SDZ-PMX-622, selectin antagonists (e.g., sulfated glycolipid cell adhesion inhibitors), thrombin inhibitors (e.g., GS-522), TNF receptor-Ig, tumor necrosis factor antagonists (e.g., anti-TNF MAbs, MAK-195F, TBP-I, Yeda, rhTNFbp, CDP-571, and the like), tumor necrosis factor alpha antagonists (e.g., E-5531), and the like.

Still further treatments which lead to the overproduction of nitric oxide include administration of agents for the treatment of multiple sclerosis, such as 4-aminopyridine, 15±deoxyspergualin, ACTH, amantadine, antibody adjuvants (e.g., poly-ICLC, poly-IC+poly-L-lysine+carboxymethylcellulose, and the like), anti-cytokine MAb (e.g., CDP-835), anti-inflammatory agents (e.g., CY-1787, CY-1503, and the like), anti-selectin MAb (e.g., CY-1787), anti-TCR MAb (e.g., NBI-114, NBI-115, NBI-116, and the like), bacloten, bethanechol chloride, carbamazepine, carbohydrate drugs (e.g., CY-1503), clonazepam, CNS and immune system function modulators (e.g., NBI-106, NBI-107, and the like), cyclophosphamide, cyclosporine A, cytokines (e.g., IFN-α, alfaferone, IFN-β 1b, betaseron, TGF-β2, PEG-TGF-β2, betakine, IFN-β/Rebif, frone, interferon-β, IFN-β, and the like), CD4+T cell inhibitors (e.g., AnergiX), CD28 antagonists (e.g., B7-1, B7-2, CD28, and the like), direct cytotoxicity therapi s (e.g., benzoporphyrin derivative (BPD)), FK-506, growth factors (e.g., glial growth factor, GGF, nerve growth factors, TGF-β2, PEG-TGF-β2, betakine, and the like), humanized MAb (e.g., anti-IFN-γMAb, smart anti-IFN-γMAb, anti-Tac antibody, smart anti-Tac antibody, and the like), humanized anti-CD4 MAb (e.g., anti-CD4 MAb, centara, and the like), hydrolase stimulants (e.g., castanospermine), IFN-α, IFN-γ antagonists (e.g., anti-IFN-γMAb, smart anti-IFNγMAb, and the like), IL-2 antagonists (e.g., tacrolimus, FK-506, FR-900506, Fujimycin, Prograf, IL-2 fusion toxin, DAB_{389}IL-2, and the like), IL-4 antagonists (e.g., IL-4 fusion toxin, DAB_{389}IL-4, and the like), immune-mediated neuronal damage inhibitors (e.g., NBI-114, NBI-115, NBI-116, and the like), immunoglobins, immunostimulants (e.g., poly-ICLC, edelfosine, ALP, ET-18-OCH3, ET-18-OME, NSC-24, poly-IC+poly-L-lysine+carboxymethylcellulose, and the like), immunosuppressants (e.g., azathioprine, AI-100 animal protein, rDNA human protein AI-101, peptide, AI-102, castanospermine, tacrolimus, FK-506, FR-900506, Fujimycin,

Prograf, anti-leukointegrin MAb, Hu23F2G, primatized anti-CD4 antibody, CE9.1, Galaptin 14-1, GL14-1, Lectin-1, recombinant IML-1, linomide, roquinimex, LS-2616, transcyclo-pentanyl purine analogs, MS-6044, spanidin, 15-deoxyspergualin, deoxyspurgiline, gusperimus HCL, NSC-356894, NKT-01, TCR, CD3/Ti, cyclosporine, OL-27-400, SandImmune, Human IL-10, monogens, anti-TCR MAbs, TCAR MAbs, Monogen TM19, Monogen TM27, Monogen TM29, Monog n TM31, peptigen TP12, anti-CD4 MAb, cantara, immunophilins, VX-10367, VX-10393, VX-10428, synthetic basic copolymer of amino acids, copolymer-1, COP-1, T lymphocyte immunofusion (TIF) protein, cyclophosphamide, and the like), integrin antagonists (e.g., anti-integrin monoclonal antibodies, AN-100225, AN-100226, and the like), interferon agonists (e.g., poly-ICLC, poly-IC+poly-L-lysine+carboxymethylcellulose, and the like), interferon-β-1b, isoprinosine, IV methylprednisolone, macrolides (e.g., tacrolimus, FK-506, FR-900506, Fujimycin, Prograf, and the like), MAO B inhibitors (e.g., selegiline, Parkinyl, and the like), methotrexate, mitoxantrone, muscle relaxants (e.g., RGH-5002), muscarinic antagonists (e.g., RGH-5002), neurosteroids (e.g., NBI-106, NBI-107, and the like), octapeptides (e.g., peptide T), oxybutinin chloride, oxygen free radical antagonists (e.g., tetrandrine, biobenzylisoquinoline alkaloid, and the like), peptide agonists (e.g., peptide T), phenoxybenzamine, phospholipase C inhibitors (e.g., edelfosine, ALP, ET-18-OCH3, ET-18-OME, NSC-24, and the like), photodynamic therapies (e.g., benzoporphyrin derivative (BPD)), plasmapheresis, platelet activating factor antagonists (e.g., ginkgolide B, BN-52021, and the like), potassium channel antagonists (e.g., aminodiaquine, EL-970, and the like), propranolol, prostaglandin synthase inhibitors (e.g., sulfasalazin , salazosulfa-pyridine, PJ-306, SI-88, azulfidine, salazopyrin, and the like), protease antagonists (e.g., ginkgolide B, BN-52021, and the like), recombinant soluble IL-1 receptors, spergualin analogs (e.g., spanidin,

15-deoxyspergualin, deoxyspurgiline, gusperimus HCL, NSC-356894, NKT-01, and the like), TCR peptide decoys (e.g., NBI-114, NBI-115, NBI-116, and the like), TCR peptidomimetic decoys (e.g., NBI-114, NBI-115, NBI-116, and the like), TCR peptide vaccines (e.g., AI-208 (Vβ6.2/6.5 phenotype)), selectin antagonists (e.g., lectin-1, recombinant IML-1, and the like), soluble TNF receptor I, TCARs (e.g., TCR, CD3/Ti, peptigen TP12, and the like), TNF antagonists (e.g., thalidomide, TNF inhibitors, and the like), tricyclic antidepressants, and the like.

Additional treatments which lead to the overproduction of nitric oxide include administration of organ transplantation agents, such as anti-CD25 MAbs, anti-Tac antibodies, anti-TNF MAb (e.g., CDP571), apoptosin, azathioprines (e.g., imuran), BCX-34, CA3, CD28, complement inhibiting factors (e.g., CD59), CTLA4Ig, cyclosporines (e.g., CsA), FK-506/rapamycin binding proteins (FKBP), glucocorticoids, humanized version of OKT3 (e.g., huOKT3-185), hydroorotate dehydrogenase inhibitors (e.g., Brequinar), orthoclone OKT3 (e.g., IgG2a anti-T cell murine monoclonal antibody, muromonab-CD3, and the like), rapamycins (e.g., AY-22989), streptomyces isolates (e.g., FR-900520, FR-900523, and the like), and the like.

Additional treatments which lead to the overproduction of nitric oxide include administration of agents for the treatment of systemic lupus erythematosus (SLE), such as androgen-derived steriods (e.g., Org-4094), anti-CD4 humanized antibodies, anti-DNA/V-88, anti-idiotypic murine MAb (e.g., anti-idiotypic antibody to 3E10/MAb1C7), CD2 antagonists (e.g., CD2), complement inhibitors (e.g., recombinant MCP-based complement inhibitors), cyclosporines (e.g., Sandimmune, cyclosporine analog, OG-37325, cyclosporin-G, NVal-CyA, and the like), cytokines (e.g., IL-4 fusion toxin), cytokine receptor antagonists (e.g., immunomodulatory cytokines), E-selectin

antagonists (e.g., anti-ELAM, CY-1787, and the like), FK506/tacrolimus (e.g., Prograf), hypercalcemic agents (e.g., KH-1060), IFN-γ antagonists (e.g., anti-IFN-γ MAb, smart anti-IFN-γ MAb, and the like), IL-1β converting enzyme inhibitors (ICE), IL-2 produced by E. coli (e.g., celmoleukin, IL-2, TGP-3, Celeuk, and the like), immunoglobulins (e.g., anti-ELAM, CY-1788, humanized CY-1787, and the like), immunostimulants (e.g., thymotrinan, RGH-0205, TP3, and the like), immunosuppressants (e.g., Rapamycin, AY-22989, NSC-226080, NSC-606698, anti-CD4, T-cell inhibitor, anti-tac MAb, smart anti-tac MAb, Migis (membrane immunoglobulin-isotope specific) antibodies, SM-8849, immunophilins, VX-10367, VX-10393, VX-10428, mycophenolate mofetil, ME-MPA, RS-61444, cyclosporine, OL-27-400, Sandimmune, IL-4 fusion toxin, trypanosomal inhibitory factor (TIF), T-cell receptor, CD3/Ti, Org-4094, anti-TBM, CP 17193, Leflunomide/A-77-1726, ELAM-1, AnergiX, Spanidin, 15-deoxyspergualin, deoxyspurgiline, gusperimus hydrochloride, NSC-356894, NKT-01, Roquinimex, LS-2616, linomide, LJP-394, CD-59 antigen, and the like), immunotoxins (e.g., Zolimomab aritox, xmmly-h65-rta, xomazyme-lym/CD5-Plus, OrthoZyme-CD5+, XomaZyme-H65-rta, Xomazyme-CD5 Plus, and the like), intravenous immunoglobulins (e.g., IVIG), integrin antagonists (e.g., integrin blockers), Migis™ antibodies, monoclonal antibody therapeutics, murine MAb (e.g., anti-SLE vaccine, MAb 3E10, and the like), primatized anti-CD4 antibodies (e.g., CE9.1), protease inhibitors (e.g., matrix metalloprotease (MMP) inhibitors, stromelysin, and the like), protein synthesis antagonists (e.g., anti-CD6-bR, anti-T12-bR, oncolysin CD6, and the like), purine nucleoside phosphorylase inhibitors (e.g., BCX-25, BCX-14, and the like), selectin antagonists (e.g., CY1503, Cylexin, and the like), spergualin analogues (e.g., Spanidin, 15-deoxyspergualin, deoxyspurgiline, gusperimus hydrochloride, NSC-356894, NKT-01, and the like), T cell

inhibitors (e.g., AnergiX), tumor necrosis factor (TNF) antagonists, and the like.

Additional treatments which lead to the overproduction of nitric oxide include administration of agents for the treatment of Alzheimer's disease, such as ACh release enhancers (e.g., T-588 (benzothiophene derivative)), acetylcholine release stimulants (e.g., DUP-996 and analogues), AMPA agonists (e.g., AMAlex, Isoxazole compound series, and the like), AMPA GluR agonist (e.g., IDRA-21 [7-chloro-3-methyl-3,4-dihydro-2H-1,2,4-benzothiadiazinine]), AMPA GluR antagonists (e.g., S-18986 and related quinolone derivatives), anticholinesterases (e.g., E-2020), Ca-antagonists (e.g., NS-649, spider venom-derived ICM peptides and analogues, substituted 2-aminoindanes compound series, and the like), combined anticholinesterase and muscarinic AChR antagonists (e.g., PD142676), K-channel blockers (e.g., Trans-R-4-(4-methoxyphenyl-methyl) cyclohexylanine and analogues, margatoxin-based functional and/or structural analogues, and the like), MI muscarinic receptor agonists (e.g., Xanomeline), NMDA antagonists (e.g., certain indole derivatives, (R-(R^1,S^1))-α-(4-hydroxyphenyl)-beta-methyl-4-(phenylmenthyl)-1-piperidinepropanol and analogues thereof, and the like), nicotinic AChR agonists (e.g., ABT-418 [isoxazole, 3-meth-5-(1-meth-2-pyrrolidinyl)], and the like), and the like.

Additional treatments which lead to the overproduction of nitric oxide include administration of agents for the treatment of psoriasis, such as 5-LO inhibitors (e.g., Wy-50295, Wy-49232, Lonapalene, RS-43179, MK-886, L-663536, ETH-615, DUP-654, Zileuton, epocarbazolin-A, A-64077, and the like), 5-LO/CO inhibitors (e.g., BF-397, Tenidap, CP-309, CP-66248, and the like), angiogenesis inhibitors (e.g., platelet factor 4), anticancer antibiotic (e.g., AGM-1470, TNP-470, and the

like), anti-inflammatory cytochrome P450 oxidoreductase inhibitors (e.g., DuP-630, DuP-983, and the like), antiproliferative compounds (e.g., Zyn-Linker), arachidonic acid analogues (e.g., CD581, CD554, and the like), arachidonic acid antagonists (e.g., Lonopalene, RS-43179, triamcinolone acetonide with penetration enhancer Azone, betamethasone dipropionate steroid wipe, G-202, Halobetasol propionate, ultravate, Halometasone, C-48401-Ba, Sicorten, and the like), beta-glucan receptor antagonists, betamethasone steroid wipes, calcium metabolic moderators (e.g., Tacalcitol, Bonealfa, TV-02 ointment, Ro-23-6474, KH-1060, Calcipotriol, BMS-181161, BMY-30434, Dovonex, Divonex, and the like), CD4 binding inhibitors (e.g., PIC 060), cell adhesion compounds (e.g., CY-726, VCAM-1, ELAM-1, ICAM, and the like), cell adhesion inhibitors (e.g., selectin inhibitor, GM-1930, and the like), cellular aging inhibitors (e.g., Factor X), corticosteroids (e.g., Halobetasol propionate, ultravate, Halometasone, C-48401-Ba, Sicorten, and the like), cyclosporin analogues (e.g., IMM-125), dihydrofolate reductase inhibitors (e.g., G-301, dichlorobenzoprim, methotrexate, methotrexate in microsponge delivery system, and the like), E-selectin inhibitors (e.g., ISIS 4730), endogenous active form of vitamin D_3 (e.g., Calcitriol, Du-026325, and the like), fibroblast growth factor antagonists (e.g., Saporin mitotoxin, Steno-Stat, and the like), fumagillin analogues (e.g., AGM-1470, TNP-470, and the like), G-proteins and signal transduction compounds (e.g., CPC-A), gel formulations for acne (e.g., nicotinamide, N-547, Papulex, and the like), growth hormone antagonists (e.g., Octreotide, Sandostatin, Lanreotide, angiopeptin, BIM-23014, Somatuline, and the like), humanized antibodies (e.g., anti-CD4 antibody), hydroorotate dehydrogenase inhibitors (e.g., Brequinar sodium, bipenquinate, DuP-785, and the like), ICAM-1 inhibitors (e.g., ISIS 939), IL-1 and other cytokine inhibitors (e.g., Septanil), IL-1 converting ezyme inhibitors, IL-1 receptor antagonists (e.g., Antril),

IL-2 antagonists (e.g., Tacrolimus, Prograf, FK-506, and the like), IL-2 receptor-targeted fusion toxins (e.g., DAB389IL-2), IL-8 receptors, immunostimulants (e.g., Thymopentin, Timunox, and the like), immunosuppressants (e.g., XomaZyme-CD5 Plus, cyclosporine, Sandimmune, SR-31747, anti-CD11, 18 MAb, Tacrolimus, Prograf, FK-506, FK-507, and the like), immunosuppressive agents targeting FK506 (e.g., immunophilins, VX-10367, VX-10428, and the like), immunotoxins MAb directed against CD antigen (e.g., XomaZyme-CD5 Plus), leukotriene antagonists (e.g., Sch-40120, Wy-50295, Wy-49232, and the like), leukotriene B4 antagonists (e.g., SC-41930, SC-50605, SC-48928, ONO-4057, LB-457, LY-255283, LY-177455, LY-223982, LY-223980, LY-255253, and the like), leukotriene synthesis inhibitors (e.g., MK-886, L-663536, and the like), lipase clearing factor inhibitors (e.g., 1-docosanol, lidakol, and the like), lipid encapsulated reducing agent (e.g., Dithranol), liposomal gel (e.g., Dithranol), LO inhibitors (e.g., CD581, CD554, Masoprocol, Actinex, and the like), lithium succinate ointments (e.g., lithium salts, Efalith, and the like), LO/CO inhibitors (e.g., P-8892, P-8977, CHX-108, FPL-62064, and the like), membrane integrity agonists (e.g., lithium salts, Efalith, and the like), microtubule inhibitors (e.g., Posophyliotoxin-containing compound, Psorex, and the like), octapeptide somatostatin analogues (e.g., Lanreotide, angiopeptin, BIM-23014, Somatuline, and the like), oligonucleotides (e.g., ISIS 4730, ISIS 3801, ISIS 1939, IL-1 inhibitors, and the like), peptide agonists (e.g., octapeptide, peptide T, and the like), PKC inhibitors, phospholipase A2 compounds, pospholipase D compounds, photodynamic anticancer agents (e.g., 5-aminolevulinic acid, 5-ALA, and the like), photodynamic therapies (e.g., benzoporphyrin derivatives, synthetic chlorins, synthetic porphyrins, EF-9, and the like), photosensitizer (e.g., Porfirmer sodium), PKC inhibitors (e.g., Safingol, Kynac, and the like), platelet activating factor antagonists (e.g., TCV-309), platelet

aggregation inhibitors (e.g., CPC-A), prodrug NSAIDs (e.g., G-201), prostaglandin agonists (e.g., eicosapentaenoic acid + gamma-linolenic acid combination, Efamol Marine, and the like), protein inhibitors (e.g., SPC-103600, SPC-101210, and the like), protein kinase C (PKC) inhibitors (e.g., Ro-31-7549, Ro-31-8161, Ro-31-8220, and the like), protein synthesis antagonists (e.g., Calcitriol, Du-026325, LG-1069, LG-1064, AGN-190168, Namirotene, CBS-211A, and the like), purine nucleoside phosphorylase inhibitors (e.g., BCX-34), radical formation agonists (e.g., benzoporphyrin derivatives), recombinant antileukoproteinases (e.g., ALP-242), retinoids (e.g., BMY-30123, LG-1069, LG-1064, and the like), retinoid derivatives (e.g., AGN-190168), rapamycin binding proteins (FKBP) (e.g., immunophilins, VX-10367, VX-10428, and the like), second generation monoaromatic retinoids (e.g., Acitretin, Neotigason, and the like), soluble IL-1, IL-4 and IL-7 receptors, somatostatin analogues (e.g., Octreotide, Sandostatin, and the like), steroids (e.g., AGN-191743), streptomyces anulatus isolates (e.g., epocarbazolin-A), superoxide dismutase (e.g., EC-SOD-B), thymidylate synthase inhibitors (e.g., AG-85, MPI-5002, 5-FU in biodegradable gel-like matrix, 5-FU and epinephrine in biodegradable gel-like matrix, AccuSite, and the like), topical formulations (e.g., P-0751, P-0802, and the like), transglutaminase inhibitors, tyrphostin EGF receptor kinase blockers (e.g., AG-18, AG-555, and the like), VCAM-1 inhibitors (e.g., ISIS 3801), vitamin D analogues (e.g., Ro-23-6474, KH-1060, Calcipotriol, BMS-181161, BMY-30434, Dovonex, Divonex, and the like), vitamin D_3 analogues (e.g., Tacalcitol, Bonealfa, TV-02 ointment, and the like), vitamin D_3 derivatives (e.g., 1,2-diOH-vitamin D_3), and the like.

Still further treatments which lead to the overproduction of nitric oxide include administration of agents for the treatment of diabetes, such as ACE inhibitors (e.g., captopril), amylin agonists and

antagonists (e.g., Normylin™, AC137, GC747, AC253, AC625, and the like), autoimmune compounds (e.g., AI-401), capsaicins (e.g., Zostrix-HP), cell regulators (e.g., protein kinase C inhibitors, Balanol, and the like), domperidones (e.g., Motilium®), fluvastatins (e.g., Lescol), FOX 988, fusion toxins (e.g., DAB_{389}IL-2, DAB_{486}IL-2, and the like), gene therapies (e.g., Transkaryotic Therapies), glucagons (e.g., recombinant yeast glucagon), IL-10 compounds, iloprost, immunosuppressives (e.g., tacrolimus, Prograf, FK-506, and the like), insulin analogs (e.g., AI-401, Nu-Insulin compounds, Humulin, Iletin, Humalog™, LYs-Pro, Amaryl, and the like), insulin-like growth factors (e.g., Chiron/Ciba-Geigy compounds, Fujisawa compounds, Genentech compounds, and the like), insulinotropins (e.g., Pfizer/Scios Nova compounds), nerve growth factors (e.g., Genentech compounds), oral hypoglycemics (e.g., AS-6, glimepiride, Amaryl, CL 316,243, acarbose, miglitol, recombinant yeast glucagon, GlucaGen™, NovoNorm™, glipizide, insulinotropin, CI-991/CS-045, and the like), platelet-derived growth factors (e.g., ZymoGenetics/NovoNordisk compounds), sulfonylureas (e.g., tolbutamide, acetohexamide, tolazamide, chlorpropramide, and the like), T cell approaches (e.g., anergize, AnergiX™, Procept compounds, T cell Sciences compounds, and the like), tolrestats (e.g., Alredase®, ARI-509, and the like), and the like.

Additional treatments which lead to the overproduction of nitric oxide include the administration of agents for the treatment of stroke, such as 5-HT antagonists (e.g., Piperazine derivatives), 5-HT reuptake inhibitors (e.g., Milnacipran, Dalcipran, and the like), 5-HT 1A agonists (e.g., SR-57746A, SR-57746, and the like), 5-HT 3 agonists (e.g., SR-57227), 5-HT 4 antagonists, 5-lipoxygenase inhibitors (e.g., low MW dual 5-lipoxygenase and PAF inhibitor CMI-392), ACH agonists (e.g., Pramiracetam, Choline-L-alfoscerate, L-alpha-

glycerylphosphoryl-choline, Delecit, and the like), adenosine agonists (e.g., GP-1-4683, ARA-100, arasine analogs, and the like), adenosine A1 receptor agonists (e.g., Azaisotere, 2-chloro-N-[4 (phenylthio)-1-piperidinyl] adenosine, 2120136, and the like), adenosine reuptake inhibitors (e.g., Diphenyloxazole derivatives), adrenergic transmitter re-uptake inhibitors (e.g., Bifemelane, E-0687, MCI-2016, Alnert, Celeport, and the like), aldose reductase inhibitors (e.g., Spiro-3' pyrroline derivatives), alpha antagonists (e.g., Drotaverine acephyllinate, Depogen, and the like), alpha 2 agonists (e.g., SNAP-5083, SNAP-5608, SNAP-5682, and the like), AMPA receptor agonists (e.g., heterocyclic compound SYM-1207, heterocyclic compound SYM-1252, and the like), AMPA receptor antagonists (e.g., LY-293558, LY-215490, and the like), Ancrod/Arvin, aspirin, benzothiazoles (e.g., Lubeluzole, R87926, and the like), benzodiazepine receptor antagonists (e.g., 3-oxadiazolyl-1,6-naphthyridine derivatives, Tetracyclic imidazodiazepineseries imidazenil, FID-02-023, Ro-23-1412, and the like), blood substitutes, bradykinin antagonists (e.g., CP-0127, Bradycor, Septicor, and the like), C5a release inhibitors (e.g., protein derivative CMI-46000), calcium antagonists (e.g., Lemildipine, NB-818, NPK-1886, Trimetazidine derivatives, Iomerizine KP-2796, Diltiazem analog clentiazem maleate, TA-3090, and the like), calcium channel antagonists (e.g., nitrendipine-like compound diperdipine, YS-201, U-92032, Diltiazem derivative, 1058, SM-6586, KP-840, F-0401, D-31-D, tetrahydronaphthalene derivatives, fasudil, AT-877, H-7, HA-1044, HA-1077, Eril, darodipine, dazodipine, PY-108-068, Plimo, Dihydropy-ridine, AE 0047, GJ-0956, Lacidipine, GR-43659, GR-43659X, GX-1048, S-312-d, S-312, S-830312, Nilvadipine, FK-235, and the like), calpain inhibitors (e.g., AK-275, CX-275, and the like), carnitine palmitoyl-transferase inhibitors, carvedilol, cell adhesion molecular technology, cerebral calcium antagonist vasodilators (e.g., Nimodipine, Nimotop, and the like),

cholinesterase inhibitors (e.g., indole and indazole derivatives, Tacrine analogs, and the like), complement factor inhibitors (e.g., TK9C, protein derivative TP16, compinact A, compinact C, Factor D inhibitors, soluble, recombinant MCP-based complement inhibitors, and the like), complement inhibitors (e.g., sCRI/BRL-55730, YM-203, and the like), coronary vasodilators (e.g., Nicorandil, RP-46417, SG-75, Adancor, and the like), CPC-111, cytidyl diphosphocholine/citicholines, cytokines (e.g., NBI-117), Dexanabiol, dopamine agonists, EAA receptors, endothelin antagonists (e.g., SB 209670), endothelin receptor antagonists, excitatory amino acid agonists (e.g., acylated polyamine analogs, N-(4-hydroxyphenylpropa-noyl)-spermine analogs, and the like), excitatory amino acid antagonists (e.g., Tryptophan, 4,6-disubstituted stroke & kynurenine derivatives, NPC-17742, CPC-701, CPC-702, and the like), glutamate antagonists (e.g., Kainate quisqualate NNC-07-9202, NPC-17742, small molecule CNS-1237, NS-257, NS-072, BW-619C, CGS 19755, Riluzole, PK-26124, RP 54274, and the like), glutamate receptor antagonists (e.g., Araxin compounds, Quinoxaline derivative, YM-90K, YM-900, and the like), glycine antagonists, glycine NMDA agonists (e.g., 3-hydroxy-2,5-dioxo-1H-benz[b]azepines), glycine NMDA associated antagonists (e.g., 5,6-dihydro-1H-pyrrolo [1,2,3-de] quinoxaline-2,3-diones, Strychnine-insensitive glycine binding site of NMDA receptor L-687414, Glystasins, ACEA-2011, ACEA-3031, AC-1021, ACPC, eliprodil, and the like), growth factor antagonists (e.g., non-peptide indolocarbazole neutrophic molecules, CEP-075, and the like), GPIIb/IIIa antagonists (e.g., Peptide C68-22), hemorheological agents (e.g., Drotaverine acephyllinate, Depogen, and the like), heparin, hydroxyl radical formation inhibitors (e.g., homopiperazine derivative K-7259), hypocalcemic agents (e.g., calcitonin peptide, related to hCGRP peptide), hypothermic agents/BMY-20862, ICAM-1 compounds (e.g., Enlimomab), immunosuppressants (e.g., small molecule compounds, NBI-117, and the like), integrin

general antagonists (e.g., monoclonal antibody AN-100225, monoclonal antibody AN-100226, and the like), Interleukin-1 antagonists (e.g., cyclic nitrones), iron-dependent lipid peroxidation inhibitors (e.g., 2-(amino-methyl) chromans), lactic acid accumulation/inhibitors (e.g., small molecule CPC-211), Leukotriene B4 antagonists (e.g., Ebselen, DR-3305, PZ-25, PZ-51, RP 60931, RP 61605, and the like), lipid peroxidase inhibitors (e.g., Idebenone, Avan, and the like), low molecular weight small molecules, methyltransferase stimulants (e.g., 4-methyl benzenesulfonate, ademetionine sulfate tosilate, FO-156, Ceritan, and the like), monoamine oxidase B inhibitors (e.g., MD-280040, MD-200243, MD-280080, Lazabemide, Ro-19-6327, and the like), MS-153, MS-424, /Na^+/H^+ Na^+/Li^+ exchange inhibitors (e.g., Pyrazine derivatives), nadroparin (e.g., Fraxiparin), nafronyl/naftidrofuryl (e.g., Praxilene), nerve growth factor agonists (e.g., small molecule compounds, CNTF, BDNF, 2.5S NGF, monosialoganglioside GM1, Sigen/Sygen, and the like), neuronal calcium channel blockers (e.g., CPC-304, CPC-317, and the like), neuronal differentiation compounds (e.g., F-spondin), neuropeptide agonists (e.g., Neurotrophic Peptide Trofexin), neutrophil inhibitory factors (e.g., small molecule compounds), nitric oxide agonists (e.g., hydroxy derivative N-3393, hydroxy derivative N-3398, nicorandil, Therapicon, and the like), nitric oxide antagonists, NMDA antagonists (e.g., Spiroisoindoles/dizocilpine derivatives, Oxindole compound, CP-112116, LY-104658, LY-235959, FR-115427, Sialic acid derivative, N-palmitoyl-Betaethylglycoside neuraminic acid, ND-37, Ro-01-6794, 706, Dextrorphan, Ifenprodil analogue eliprodil, SL-82.0715, Lipophilic molecules, HU-211, Remacemide, 934-423, 12495, 12859, 12942AA, Selfotel, CGS-19755, SDZ-EAA-494, CGP-40116, CGP-37849, CGP-39551, CGP-43487, and the like), NMDA antagonist-partial agonists (e.g., Conantokin G peptide SYM-1010), NMDA channel blockers (e.g., Aptiganel, CERESTAT, CNS 1102, and the

like), NMDA receptor antagonists, NMDA receptor subtypes (e.g., Kainate quisqualate NNC-07-9202), non-competitive NMDA antagonists (e.g., FPL-15896), non-ionic copolymer RheothRx, nootropic/acetylcholine agonists (e.g., Oxiracetam, CT-848, Neuractiv, and the like), norepinephrine inhibitors (e.g., Midalcipran), N-type calcium channel antagonists (e.g., NS-626, NS-638, and the like), opioid antagonists (e.g., Nalmefene, nalmetrene, JF-1, ORF-11676, Cervene, Incystene, and the like), opioid kappa receptor agonists (e.g., acrylacetamide enadoline, CI-997, and the like), organoselenims (e.g., Ebselen, DR-3305, PZ-25, PZ-51, RP 60931, RP 61605, and the like), oxygen scavengers (e.g., Tirilazad mesylate, Lazaroids, Freedox, and the like), PA2 inhibitors (e.g., Sphphospholipase A2 inhibitor), PAF antagonists (e.g., nupafant, BB-2113, and the like), partial glycine NMDA agonists (e.g., ACPC), peptide/GPIIb/IIIa antagonists (e.g., Integrelin), peptidic neuron-specific calcium channel antagonists (e.g., SNX-111), phosphodiesterase inhibitors (e.g., Xanthine derivatives, propentofylline, Hoe-285, Hextol, and the like), phospholipase A2 inhibitors (e.g., small organic molecule CEP-217), plasminogen activators (e.g., r-ProUK (recombinant pro-urokinase), platelet-activating factor antagonists (e.g., UK-74505), platelet adhesion inhibitors (e.g., Peptide), platelet aggregation antagonists (e.g., cilostazol, peptide agents, GPHb-IIIA inhibitor, TP-9201, and the like), platelet aggregation inhibitors (e.g., Diaminoalkanioic acid derivatives), potassium channel agonists (e.g., Nicorandil, RP-46417, SG-75, Adancor, and the like), prolyl endopeptidase (PEP) inhibitors (e.g., JTP-4819), protein kinase C inhibitors (e.g., monosialoganglioside derivative Liga-20), proteolytic enzyme inhibitors (e.g., Protease nexin-1, Incyte, PN-1, PN-2, Nafamostat, FUT-175, Duthan, Futhan, and the like), pyrimidine derivatives, Quinolizine derivatives (e.g., KF-17329, KF-19863, and the like), radical formation antagonists (e.g., EPC-K1), recombinant

tissue plasminogen activators (e.g., alteplase, Activase, and the like), Schwann cell derived molecules/promoters, sigma antagonists (e.g., Sigma ligand), sigma receptor antagonists (e.g., tetrahyropyridinyl-isoxazolines, isoxazoles PD-144418, and the like), sodium/calcium channel modulators (e.g., Lifarizine, RS-87476, and the like), sodium channel antagonists, streptokinase (e.g., Streptase), substituted guanadine (e.g., small molecule CNS-1237), superoxide dismutase stimulants (e.g., PEG conjugated enzyme superoxide dismutase/Dismutec, PEG-SOD, and the like), thrombin inhibitors, (e.g., non-peptide), thromboxane synthase inhibitors (e.g., Linotroban, HN-11500, and the like), thyrotropin-releasing hormone agonists (e.g., TRH agonists, Protirelin analogthymoliberin, RX-77368, and the like), ticlopidine (e.g., Ticlid), TJ-8007, TRH agonists (e.g., Thyrotropin releasing hormones, JTP-2942, and the like), trilazard, urokinase (e.g., Abbokinase), w-conopeptide (e.g., SNX-111), warfarin (e.g., Coumadin), and the like.

Accordingly, presently preferred indications for treatment in accordance with the present invention include septic shock, ischemia, ulcers, ulcerative colitis, diabetes, arthritis, asthma, Alzheimer's disease, Parkinson's disease, multiple sclerosis, cirrhosis or allograft rejection, and the like.

In accordance with a particular aspect of the present invention, the nitric oxide scavenging agent is administered in combination with one or more of the above-described agents, optionally including an antibiotic (e.g., gentamicin, tobramycin, amikacin, piperacillin, clindamycin, cefoxitin or vancomycin, or mixtures thereof), a vasoactive agent (e.g., a catecholamine, noradrenaline, dopamine or dobutamine), or mixtures thereof. In this way, the detrimental side effects of many of the above-noted pharmaceutical agents and/or the indications they are

designed to address (e.g., systemic hypotension) can be prevented or reduced by co-administration of a combination reagent including a nitric oxide scavenger.

Those of skill in the art recognize that the combination of an agent capable of inactivating species which induce the expression of inducible nitric oxide (or an agent capable of inhibiting the production of such species), and nitric oxide scavengers described herein can be delivered in a variety of ways, such as, for example, orally, intravenously, subcutaneously, parenterally, rectally, by inhalation, and the like.

Since individual subjects may present a wide variation in severity of symptoms and each drug has its unique therapeutic characteristics, the precise mode of administration, dosage employed and treatment protocol for each subject is left to the discretion of the practitioner.

In accordance with still another embodiment of the present invention, there are provided physiologically active composition(s) comprising a "therapeutic agent" (as described herein) and a nitric oxide scavenging compound (e.g., a compound having the structure I, as described above), in a suitable vehicle rendering said composition amenable to oral delivery, transdermal delivery, intravenous delivery, intramuscular delivery, topical delivery, nasal delivery, and the like.

Depending on the mode of delivery employed, the above-described compositions can be delivered in a variety of pharmaceutically acceptable forms. For example, the above-described compositions can be delivered in the form of a solid, solution, emulsion, dispersion, micelle, liposome, and the like.

Pharmaceutical compositions of the present invention can be used in the form of a solid, a solution, an emulsion, a dispersion, a micelle, a liposome, and the like, wherein the resulting composition contains one or more each of the nitric oxide scavenging and therapeutically active compounds contemplated for use in the practice of the present invention, as active ingredients thereof, in admixture with an organic or inorganic carrier or excipient suitable for enteral or parenteral applications. The active ingredients may be compounded, for example, with the usual non-toxic, pharmaceutically acceptable carriers for tablets, pellets, capsules, suppositories, solutions, emulsions, suspensions, and any other form suitable for use. The carriers which can be used include glucose, lactose, gum acacia, gelatin, mannitol, starch paste, magnesium trisilicate, talc, corn starch, keratin, colloidal silica, potato starch, urea, medium chain length triglycerides, dextrans, and other carriers suitable for use in manufacturing preparations, in solid, semisolid, or liquid form. In addition auxiliary, stabilizing, thickening and coloring agents and perfumes may be used. The active compounds (i.e., "therapeutic agents" and nitric oxide scavenging compounds (e.g., compounds of structure I as described herein)) are included in the pharmaceutical composition in an amount sufficient to produce the desired effect upon the target process, condition or disease.

Pharmaceutical compositions containing the active ingredients contemplated herein may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known in the art for the manufacture of pharmaceutical compositions. In addition, such compositions may contain one or more agents selected

from a sweetening agent (such as sucrose, lactose, or saccharin), flavoring agents (such as peppermint, oil of wintergreen or cherry), coloring agents and preserving agents, and the like, in order to provide pharmaceutically elegant and palatable preparations. Tablets containing the active ingredients in admixture with non-toxic pharmaceutically acceptable excipients may also be manufactured by known methods. The excipients used may be, for example, (1) inert diluents such as calcium carbonate, lactose, calcium phosphate, sodium phosphate, and the like; (2) granulating and disintegrating agents such as corn starch, potato starch, alginic acid, and the like; (3) binding agents such as gum tragacanth, corn starch, gelatin, acacia, and the like; and (4) lubricating agents such as magnesium stearate, stearic acid, talc, and the like. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract, thereby providing sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated by the techniques described in the U.S. Pat. Nos. 4,256,108; 4,160,452; and 4,265,874, to form osmotic therapeutic tablets for controlled release.

In some cases, formulations for oral use may be in the form of hard gelatin capsules wherein the active ingredients are mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate, kaolin, or the like. They may also be in the form of soft gelatin capsules wherein the active ingredients are mixed with water or an oil medium, for example, peanut oil, liquid paraffin, or olive oil.

The pharmaceutical compositions may be in the form of a sterile injectable suspension. This suspension may be formulated according to known methods using suitable

dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides, fatty acids (including oleic acid), naturally occurring vegetable oils like sesame oil, coconut oil, peanut oil, cottonseed oil, etc., or synthetic fatty vehicles like ethyl oleate or th like. Buffers, preservatives, antioxidants, and the like can be incorporated as required.

Compositions contemplated for use in the practice of the present invention may also be administered in the form of suppositories for rectal administration of the active ingredients. These compositions may be prepared by mixing the active ingredients with a suitable non-irritating excipient, such as cocoa butter, synthetic glyceride esters of polyethylene glycols (which are solid at ordinary temperatures, but liquify and/or dissolve in the rectal cavity to release the active ingredients), and the like.

Since individual subjects may present a wide variation in severity of symptoms and each active ingredient has its unique therapeutic characteristics, it is up to the practitioner to determine a subject's response to treatment and vary the dosages accordingly.

Typical daily doses of nitric oxide scavengers, in general, lie within the range of from about 10 μg up to about 100 mg per kg body weight, and, preferably within the range of from 50 μg to 10 mg per kg body weight and can be administered up to four times daily. The daily IV dose lies within the range of from about 1 μg to about 100 mg

per kg body weight, and, preferably, within the range of from 10 μg to 10 mg per kg body weight.

In general, the dosage of nitric oxide scavenger employed in the practice of the present invention falls in the range of about 0.01 mmoles/kg body weight of the subject/hour up to about 0.5 mmoles/kg/hr.

The invention will now be described in greater detail by reference to the following non-limiting examples.

Example 1

Wistar rats (male, 230-300 g) were supplied by Simonson Laboratories (Gilroy, CA).

Lipopolysaccharide (LPS; S. typhosa, endotoxin) was obtained from Sigma (St. Louis, MO).

N-Methyl-D-glucamine and carbon disulfide were obtained from Aldrich (Milwaukee, WI). *N*-Methyl-D-glucamine dithiocarbamate (MGD) was synthesized by following the method of Shinobu et al. (*Acta Pharmacol. Toxicol.* 54:189-194 (1984)).

Example 2

As described previously (see Lai and Komarov in *FEBS Lett.* 345:120-124 (1994)), one [$(MGD)_2$/Fe] complex binds to one molecule of nitric oxide to form a [$(MGD)_2$/Fe-NO] complex. Whereas free nitric oxide is a potent vasodilator, nitric oxide bound to [$(MGD)_2$/Fe] is not. The resulting complex is then excreted from the body in the urine, thereby reducing *in vivo* nitric oxide levels.

The effects of [$(MGD)_2$/Fe] treatment on the mean arterial pressure of endotoxemia in rats are shown in

Figure 1. When rats were treated with lethal doses of LPS, the mean arterial pressure dropped gradually with time and reached 75 mm Hg at the end of 2 hours. In controls, when the animals were infused with saline, their mean arterial pressure remained very low; indeed, 11 out of 16 animals died before the end of the experiments. On the other hand, when the LPS-treated animals were infused with [$(MGD)_2$/Fe], their mean arterial pressure gradually restored to normal levels, and only 3 out of 16 animals died before the end of the experiments. Therefore, infusions of [$(MGD)_2$/Fe] can not only restore blood pressure, but also reduces the mortality rate in endotoxin induced septic shock rats.

In summary, [$(MGD)_2$/Fe] is potentially useful for the treatment of systemic hypotension (extreme drop in blood pressure), caused by abnormally elevated levels of nitric oxide; a condition which has been associated with many inflammatory and infectious diseases. In addition, [$(MGD)_2$/Fe] has been shown to be safe inasmuch as the animals survived after injections of up to 1% of their body weight without apparent side effects (Lai and Komarov, supra).

Example 3

As previously described (see Komarov and Lai in *Biochim. Biophys. Acta* **1272**:29-36 (1995)), subcutaneous administration of the [$(MGD)_2$/Fe] complex reduced *in vivo* ·NO levels in LPS-treated mice. Since excessive ·NO production is known to induce systemic hypotension, injections of the [$(MGD)_2$/Fe] complex that reduce *in vivo* ·NO levels should also restore blood pressure in hypotensive animals induced by LPS treatment. To test this idea, experiments were carried out to determine the effects of administration of the [$(MGD)_2$/Fe] complex on the blood pressure of the hypotensive rats induced by LPS challenge.

Thus, mal Wistar rats (230-300 g) fasted overnight were anesthetized with thiobutabarbital (Inactin, 100 mg/kg, i.p.). A catheter was implanted in the femoral vein for drug infusions. The femoral artery was cannulated for continuous blood pressure measurement. Rats were injected with an i.v. bolus dose of LPS (S.Typhosa endotoxin, 4 mg/kg). Two hours after LPS challenge, rats were then subjected to one of the following treatments:

(a) Control, saline infusion- 1.0 ml saline i.v. injection followed by 1.0 ml/hr of saline infusion for 2.0 hours,

(b) [$(MGD)_2$/Fe] (at a ratio of 2-to-0.4)-0.1 mmole/kg i.v. bolus injection followed by 0.1 mmole/kg infusion for 2.0 hours,

(c) [$(MGD)_2$/Fe] (at a ratio of 2-to-0.2)-0.1 mmole/kg i.v. bolus injection followed by 0.1 mmole/kg infusion for 2.0 hours, and

(d) [$(MGD)_2$/Fe] (at a ratio of 2-to-0)-0.1 mmole/kg i.v. bolus injection followed by 0.1 mmole/kg infusion for 2.0 hours.

The results of mean arterial pressure (MAP) measurement as a result of each of these treatments are summarized in Table 1.

Table 1

Effects of various ratios of [$(MGD)_2$/Fe] treatment on the mean arterial pressure (MAP in mmHg) in lipopolysaccharide (LPS)-induced shock rats

Conditions[1]	Baseline[2] (mean±SEM)	2 hrs after LPS Exposure	2.0 hrs after Treatment
a) Control saline (n=16)[3]	96±2	77±2	76±7
b) [$(MGD)_2$/Fe] (2/0.4)[4] (n=16)	95±3	75±2	95±3
c) [$(MGD)_2$/Fe] (2/0.2) (n=9)	98±2	75±3	89±4
d) MGD (2/0) (n=9)	99±4	71±2	94±6

[1] Experimental conditions were as described in the text.
[2] The values of MAP prior to LPS treatment.
[3] n, the number of animals in each group.
[4] [$(MGD)_2$/Fe] (2/0.4) is defined as the ratio of [$(MGD)_2$/Fe] to be 2-to-0.4.

The MAP of anesthetized rats was in the range of 96 to 99 mmHg. Two hours after LPS treatment, the MAP decreased to between 71 and 77 mmHg, which is indicative of the onset of systemic hypotension, caused by abnormally elevated levels of nitric oxide, as also shown in Figure 1. While the 2.0 hr saline infusion did not change the MAP, infusions of [$(MGD)_2$/Fe] complex at various ratios, ranging from 2-to-0.4 (MGD to Fe) to 2-to-0 (MGD to Fe), restored the blood pressure to 89-95 mmHg (Table 1). These results suggest that the i.v. infusion of MGD either with or without added iron (Fe), can restore blood pressure in hypotensive rats induced by LPS challenge (Table 1).

Since MGD does not bind ·NO, it is speculated that the restoration of the MAP by MGD infusion may be

attributed to the MGD chelation of cellular iron released by excess ·NO production, which is known to attack cellular iron-containing proteins and result in cellular iron loss during sepsis or septic shock (see, for example, Kim et al., in *J. Biol. Chem.* 270:5710-5713 (1995)).

This example shows that dithiocarbamate-containing nitric oxide scavengers, such as MGD, either with or without added iron, are effective for the treatment of systemic hypotension, a condition which is associated with many inflammatory and/or infectious diseases.

Example 4

In order to test the efficacy of the combinational therapy of [$(MGD)_2$/Fe] and anti-TNF antibody for treatment of LPS-induced shock, Wistar rats are anesthetized with Ketamine/Xylazine (55 mg/kg plus 5.5 mg/kg). A catheter is implanted in the femoral vein for drug administration. The femoral artery is cannulated for continuous blood pressure measurement. The animals are allowed to recover from surgery for a period of 3 days prior to experimentation. On the day of the experiment, the conscious rats are retained in restrainers and the artery line is connected to the pressure transducer for recording. Rats are injected with an i.v. bolus dose of LPS (S. Typhosa, endotoxin, 10-20 mg/kg). Two hours after LPS challenge, rats are then subjected to one of the following treatments (8 animals in each group):

(1) Control, saline infusion - 1.0 ml saline/hr of saline infusion for 6 hours.

(2) [$(MGD)_2$/Fe] (at a ratio of 5 to 1) - 0.1 mmole/kg/hr infusion for 3 hours, followed by saline infusion for 3 hours.

(3) Anti-TNF- 7.5 mg/kg/hr infusion for 3 hours, followed by saline infusion for 3 hours.

(4) Co-infusion of [$(MGD)_2$/Fe] (0.1 mmole/kg/hr) and Anti-TNF (7.5 mg/kg/hr) for 3 hours, followed by saline infusion for 3 hours.

(5) [$(MGD)_2$/Fe] (at a ratio of 5-to-1) -0.1 mmole/kg/hr infusion for 3 hours and followed by anti-TNF (7.5 mg/kg/hr) infusion for 3 hours.

At the end of the infusion, rats are returned to their cages for observation. The 24-hr survival rates resulting from these various treatments are compared. Since a lethal dose of LPS is used, it is expected that all animals in control group 1 will die within 24 hours. Based on the results presented in Figure 1 (Example 2), it is expected that about two thirds of the rats in the treatment group (i.e., group 2, treated with [$(MGD)_2$/Fe]) will survive after 24 hours. As discussed above, in endotoxemia, TNF production is short-lived and peaks at 1-2 hours. Therefore, the infusion of anti-TNF antibodies at two hours after LPS challenge as indicated in group 3 may not be able to block the induction of the inducible nitric oxide synthase gene, which results in the production of iNOS, resulting in the overproduction of nitric oxide. In group 4, the co-infusion of anti-TNF antibodies and [$(MGD)_2$/Fe] is expected to produce a similar survival rate as that for group 2, employing [$(MGD)_2$/Fe] infusion alone. On the other hand, it is expected that the infusion of [$(MGD)_2$/Fe] for 3 hours, followed by the infusion of anti-TNF antibodies (as done with group 5) will improve the survival rate over that in group 2, because the infusion of anti-TNF antibodies at later hours would inhibit further activation of the inducible NO synthase gene, thereby reducing the further enhancement of excessive NO production.

The efficacies of combinational therapy between [$(MGD)_2$/Fe] and other therapeutic agents (such as anti-endotoxin antibodies, other anti-cytokine antibodies, anti-

cytokine receptor antibodies, and other agents, such as antibradykinin peptides, nitric oxide synthase inhibitors, and the like) can be demonstrated in a similar fashion to that described herein.

Example 5

NO production has been shown to be increased during acute cardiac allograft rejection in rats, as evidenced by elevated urinary and plasma nitrate/nitrite levels, preceding and at the time of rejection (see, for example, Winlaw et al., in Transplantation 58:1031 (1994)). Abnormally elevated NO levels appeared to be produced by activated infiltrating host macrophages and cardiac myocytes of the rejecting allograft (see, for example, Yang et al., in J. Clin. Invest. 94:714-721 (1994)).

Cyclosporin is widely used as an immunosuppressive agent to prevent allograft rejection, mainly through the inhibition of T cell activation. However, the use of cyclosporin has been associated with multiple side effects, such as, for example, nephrotoxicity, hepatotoxicity and hypertension (see, for example, Atkinson et al., in Transplantation 38:34 (1984).

Experiments were performed to evaluate the effectiveness of invention combination therapy in preventing cardiac allograft rejection in rats, employing low doses of cyclosporin and MGD/Fe. Organ donors were male Wistar-Furth (WF) strain rats weighing ~160-300 grams. Organ recipients were male Lewis (Lew) strain rats weighing ~210-340 grams. Lewis rats underwent either syngeneic (i.e., Lew-Lew) or allogeneic (i.e., WF-Lew) heterotropic cardiac transplantation to the abdominal aorta and vena cava by standard microvascular surgical techniques using sodium pentobarbital anesthesia (50 mg/kg). All cardiac transplants were observed to have good contractile

function, and there were no early deaths from surgical complications. Graft function was monitored by palpation through the abdominal wall twice daily. Allograft rejection was defined as the loss of palpable contractile activity, and was confirmed by direct inspection at laparotomy.

The MGD/Fe complex was prepared fresh daily by dissolving MGD in distilled water and then adding an appropriate amount of aqueous $FeSO_4$ to create a solution with a molar ratio of MGD/Fe of ~10:1. A sufficient volume of the MGD/Fe solution was prepared to allow subcutaneous injection. A stock solution of Cyclosporin A (CsA, Sandoz Pharma Ltd.) was prepared in commercially available olive oil. Animals received 2.5 mg/kg intramuscularly on post-operative days one to seven. This suboptimal dose ("low-dose") of CsA was used to achieve prolongation of allograft survival, without the indefinite survival which typically results when a full dose of CsA (i.e., ~10-15 mg/kg/day) is administered to the rat.

Lewis rat strain recipients received a Wistar-Furth allograft and one of the following treatments:

(1) single therapy with MGD-Fe (400 mg/kg, sc, bid) until rejection, or

(2) low-dose cyclosporin A (CsA, 2.5 mg/kg im) for seven days, or

(3) combination therapy with CsA (at the same low-dose level as used in (2)) for seven days and MGD-Fe (at the same dose level as used in (1)) for 30 days.

Body weight was used as an index of overall animal health during the study period. There was no difference in body weights at the beginning of the study, relative to the termination of the study in any of the

study groups (see Table 2). Results are expressed in the Table as mean ± SEM.

Table 2

Group	n	Body Weight, g Preoperative	Rejection
1 (Isograft)	5	289±11	305±7*
2 (Allograft, No treatment)	14	264±9	251±6
3 (Allograft, MGD-Fe)	17	243±5	234±5
4 (Allograft, CsA)	18	268±4	276±3
5 (Allograft, CsA + MGD-Fe)	11	267±7	297±8

* Body weight taken at day 30 since the isograft does not undergo rejection

In all of the study groups, there was a decrease in body weight of 8-14% by day 7 after transplant. All groups, however, displayed a weight gain after day seven, suggesting that the initial weight loss during the study period was due to the effect of surgery upon the rats, rather than the form of treatment to which the rats were subjected. Isograft controls which received no treatment exhibited similar weight trends as compared to the various treatment groups. The increase in body weight observed in the group subjected to invention combination therapy is likely the result of increased survival in the study due to improved graft survival.

Graft survival is reported herein as the mean survival time (MST±SE) in days (see Table 3).

Table 3

Group	Donor	Recp't	n	Treatment	Graft survival, days (n)†	MST†† ±SEM, days
1	LEW	LEW	5	None	>100 (5)	NA
2	WF	LEW	17	None	6.5 (11), 7.0 (1), 7.5 (3), 8.0 (1), 8.5 (1)	6.9±0.2
3	WF	LEW	16	MGD-Fe, 400 mg/kg sc bid, until rejection	9.5 (1), 10.0 (2), 10.5 (2), 11.0 (1), 11.5 (3), 12.5 (2), 13.0 (2), 13.5 (2), 14.0 (1)	11.8±0.4
4	WF	LEW	17	CsA, 2.5 mg/kg im daily x 7 days	11.0 (1), 11.5 (3), 12.0 (2), 12.5 (5), 13.0 (2), 19.5 (1), 22.0 (1), 23.0 (1), 24.0 (1)	14.5±1.1
5	WF	LEW	11	CsA, 2.5 mg/kg im daily x 7 days plus MGD-Fe, 400 mg/kg sc bid daily x 30 days	31.0 (1), 32.5 (2), 37.0 (1*), 38.0 (1), 57.0 (1), 44.5 (1), 42.0 (1), 86.0 (1**), 51.5 (1), 43.0 (1)	45.0±4.7

† (n) = number of rats
†† MST = mean survival time (in days)
* graft still functioning
** sacrificed due to paracardial abscess, graft still functioning

Acute allograft rejection occurred in 6.9±0.2 days in untreated controls. Single drug therapy with either MGD-Fe

or CsA alone significantly prolonged allograft survival, compared to untreated allografts (11.8±0.4 and 14.5±1.1 days, respectively). Combination drug therapy according to the invention, however, resulted in a dramatic prolongation of graft survival (i.e., 45.0±4.7 days).

MGD-Fe therapy was discontinued on day 30 post-transplant to determine whether indefinite survival (i.e., >100 days) was achievable. Graft function continued beyond 30 days in all 11 rats in the group receiving invention combination therapy (see Table 3). One of the rats in this group has a functioning allograft more than 50 days following cessation of combination therapy. All animals appeared healthy throughout the duration of the therapy, and there were no deaths.

In conclusion, modulation of nitric oxide levesl, especially in combination with subtherapeutic doses of standard immunosuppressive therapy, results in a dramatic prolongation of allograft survival.

While the invention has been described in detail with reference to certain preferred embodiments thereof, it will be understood that modifications and variations are within the spirit and scope of that which is described and claimed.

That which is claimed is:

1. A method for directly or indirectly treating the production of species which induce the expression of inducible nitric oxide synthase in a subject, said method comprising:

co-administering to said subject an effective amount of a combination of at least one agent capable of directly or indirectly inactivating said species, or inhibiting production of said species, and at least one nitric oxide scavenger.

2. A method according to claim 1 wherein said species is selected from cytokines, cytokine receptors, endotoxins, platelet activating factor, bradykinin, bradykinin receptor, bacteria, coagulation factors, arachidonate metabolites or nitric oxide synthase.

3. A method according to claim 1 wherein said agent is selected from anti-endotoxin agents, inhibitors of cytokine synthesis/release, anti-cytokine agents, inhibitors of the coagulation cascade, inhibitors of complement activation, inhibitors of platelet activating factor, inhibitors of arachidonate metabolism, inhibitors of nitric oxide synthase enzymes, immunosuppressive agents, diabetic therapeutic agents, therapeutic agents for inflammatory diseases or therapeutic agents for Crohn's disease therapy.

4. A method according to claim 1 wherein said agent is selected from anti-endotoxin agents, anti-cytokine agents, inhibitors of nitric oxide synthase enzymes, immunosuppressive agents or therapeutic agents for inflammatory diseases.

5. A method according to claim 1 wherein said nitric oxide scavenger is selected from the group consisting of non-heme iron-containing peptides or proteins, porphyrins, metalloporphyrins, dithiocarbamates, dimercaptosuccinic acid, phenanthroline, desferrioxamine, pyridoxal isonicotinoyl hydrazone (PIH), 1,2-dimethyl-3-hydroxypyrid-4-one (L1) and [+] 1,2-bis(3,5-dioxopiperazine-1-yl)propane (ICRF-187).

6. A method according to claim 1 wherein said nitric oxide scavenger comprises a dithiocarbamate moiety having the structure (I), optionally associated with a physiologically compatible di- or tri-valent transition metal ion, wherein structure (I) is as follows:

$$[R_1R_2N\text{-}C(S)\text{-}S^-]_x\ M^{+1,\ +2,\ +3} \qquad (I)$$

wherein:

each of R_1 and R_2 is independently selected from a C_1 up to C_{18} alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocyclic, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, alkylaryl, substituted alkylaryl, arylalkyl, substituted arylalkyl, or R_1 and R_2 can cooperate to form a 5-, 6- or 7-membered ring including N, R_1 and R_2,

x is 1 or 2, and

M is a monovalent cation when x is 1, or M is a physiologically compatible divalent or trivalent transition metal cation when x is 2.

7. A method according to claim 6 wherein the ratio of transition metal ion to dithiocarbamate moiety falls in the range of zero up to about 1:2.

8. A method according to claim 6 wherein said physiologically compatible di- or tri-valent transition metal is selected from iron, cobalt, copper or manganese.

9. A method according to claim 1 wherein said combination of at least one agent, and at least one nitric oxide scavenger is delivered orally, intravenously, subcutaneously, parenterally, rectally or by inhalation.

10. A method according to claim 1 wherein said combination of at least one agent, and at least one nitric oxide scavenger is delivered in the form of a solid, solution, emulsion, dispersion, micelle or liposome.

11. In a therapeutic process which employs an agent to inactivate materials which, directly or indirectly, induce the expression of inducible nitric oxide synthase, the improvement comprising co-administering to a patient in need thereof a nitric oxide scavenger in combination with said agent.

12. A method according to claim 11 wherein said agent is selected from anti-endotoxin agents, inhibitors of cytokine synthesis/release, anti-cytokine agents, inhibitors of the coagulation cascade, inhibitors of complement activation, inhibitors of platelet activating factor, inhibitors of arachidonate metabolism, inhibitors of nitric oxide synthase enzymes, immunosuppressive agents, diabetic therapeutic agents, therapeutic agents for inflammatory diseases or therapeutic agents for Crohn's disease therapy.

13. A composition comprising a combination of an agent capable of inactivating materials which, directly or indirectly, induce the expression of inducible nitric oxide synthase and a nitric oxide scavenger in a pharmaceutically acceptable carrier therefor.

14. A composition according to claim 13 wherein said nitric oxide scavenger is a compound having structure (I), wherein said compound having structure (I) is as follows:

$$[R_1R_2N\text{-}C(S)\text{-}S^-]_x\ M^{+1,\ +2,\ +3} \qquad (I)$$

wherein:

each of R_1 and R_2 is independently selected from a C_1 up to C_{18} alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocyclic, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, alkylaryl, substituted alkylaryl, arylalkyl, substituted arylalkyl or R_1 and R_2 can cooperate to form a 5-, 6- or 7-membered ring including N, R_1 and R_2,

x is 1 or 2, and

M is a monovalent cation when x is 1, or M is a physiologically compatible divalent or trivalent transition metal cation when x is 2.

15. A composition according to claim 14 wherein M is selected from H^+, Na^+, NH_4^+ or tetraalkyl ammonium.

16. A composition according to claim 14 wherein M is selected from Fe^{+2}, Fe^{+3}, Co^{+2}, Co^{+3}, Cu^{+2}, Mn^{+2} or Mn^{+3}.

17. A composition according to claim 14 wherein the ratio of transition metal ion to dithiocarbamate moiety falls in the range of zero up to about 1:2.

18. A composition according to claim 14 wherein:
each of R_1 and R_2 = a C_1 up to C_{12} alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl or substituted alkynyl, wherein the substituents are selected from carboxyl, -C(O)H, oxyacyl, phenol, phenoxy, pyridinyl, pyrrolidinyl, amino, amido, hydroxy, nitro or sulfuryl, and
M = Fe^{+2} or Fe^{+3}.

19. A composition according to claim 14 wherein:
R_1 = a C_2 up to C_8 alkyl or substituted alkyl, wherein said substituents are selected from carboxyl, acetyl, pyridinyl, pyrrolidinyl, amino, amido, hydroxy or nitro,
R_2 is selected from a C_1 up to C_6 alkyl or substituted alkyl, or R_2 can cooperate with R_1 to form a 5-, 6- or 7-membered ring including N, R_2 and R_1, and
M = Fe^{+2}.

20. A composition according to claim 14 wherein:
R_1 = a C_2 up to C_8 alkyl or substituted alkyl, wherein said substituents are selected from carboxyl, acetyl, amido or hydroxy,
R_2 = a C_1 up to C_4 alkyl or substituted alkyl, and
M = Fe^{+2}.

21. A composition according to claim 14 wherein said agent is selected from anti-endotoxin agents, inhibitors of cytokine synthesis/release, anti-cytokine agents, inhibitors of the coagulation cascade, inhibitors of complement activation, inhibitors of platelet activating factor, inhibitors of arachidonate metabolism, inhibitors of nitric oxide synthase enzymes, immunosuppressive agents, diabetic therapeutic agents, therapeutic agents for inflammatory diseases or therapeutic agents for Crohn's disease therapy, anti-cytokine antibodies, anti-cytokine receptor antibodies, anti-endotoxin antibodies, bradykinin antagonists, synthetic peptide blocking bradykinin receptors, bactericidal/permeability increasing protein, antibodies to platelet activating factor, or therapeutic agents for treatment of ophthalmic diseases.

22. A composition according to claim 21 wherein said anti-edotoxin agent is delected from antibodies to endotoxin, antibodies to LPS-binding protein, soluble CD14 protein, bactericidal/permeability increasing protein or polymyxin B.

23. A composition according to claim 21 wherein said inhibitor of cytokine synthesis/release is selected from phosphodiesterase inhibitors, IL-4, IL-10, IL-13, TGF-ß, aspirin, phenyl butyl nitrone or corticosteroids.

24. A composition according to claim 21 wherein said anti-cytokine agent is selected from antibodies to TNF, soluble TNF receptors, IL-1 receptor antagonists, antibodies to IL-1 receptors, antibodies to IL-6, antibodies to interferon-γ or soluble interferon-γ receptors.

25. A composition according to claim 21 wherein said inhibitor of the coagulation cascade is selected from anti-Factor XII antibodies, antibodies to C5a, C1-esterase inhibitors or soluble Cr1.

26. A composition according to claim 21 wherein said inhibitor of platelet activating factor is a PAF receptor antagonist.

27. A composition according to claim 21 wherein said inhibitor of arachidonate metabolism is selected from cyclooxygenase inhibitors, lipoxygenase inhibitors, leukotriene inhibitors, thromboxane A_2 inhibitors, or prostaglandins.

28. A composition according to claim 21 wherein said inhibitor of nitric oxide synthase enzymes is selected from N-methyl-L-arginine, ϵ-N-iminoethyl-L-lysine, aminoguanidine or S-methyl isothiourea sulfate.

29. A composition according to claim 21 wherein said immunosuppressive agent is selected from cyclosporin, OKT3, FK506, thymoglobulin or mycophenolic acid.

30. A composition according to claim 21 wherein said diabetic therapeutic agent is selected from free pancreatic islets, encapsulated pancreatic islets, oral insulin, intravenous insulin, or amylin hormone.

31. A composition according to claim 21 wherein said therapeutic agent for inflammatory disease is selected from sulfasalazine, mesalamine, corticosteroids, azathioprine, 6-mercaptopurine, or metronidazole.

32. A composition according to claim 21 wherein said therapeutic agent for inflammatory disease is a dihydropyridine calcium channel blocker.

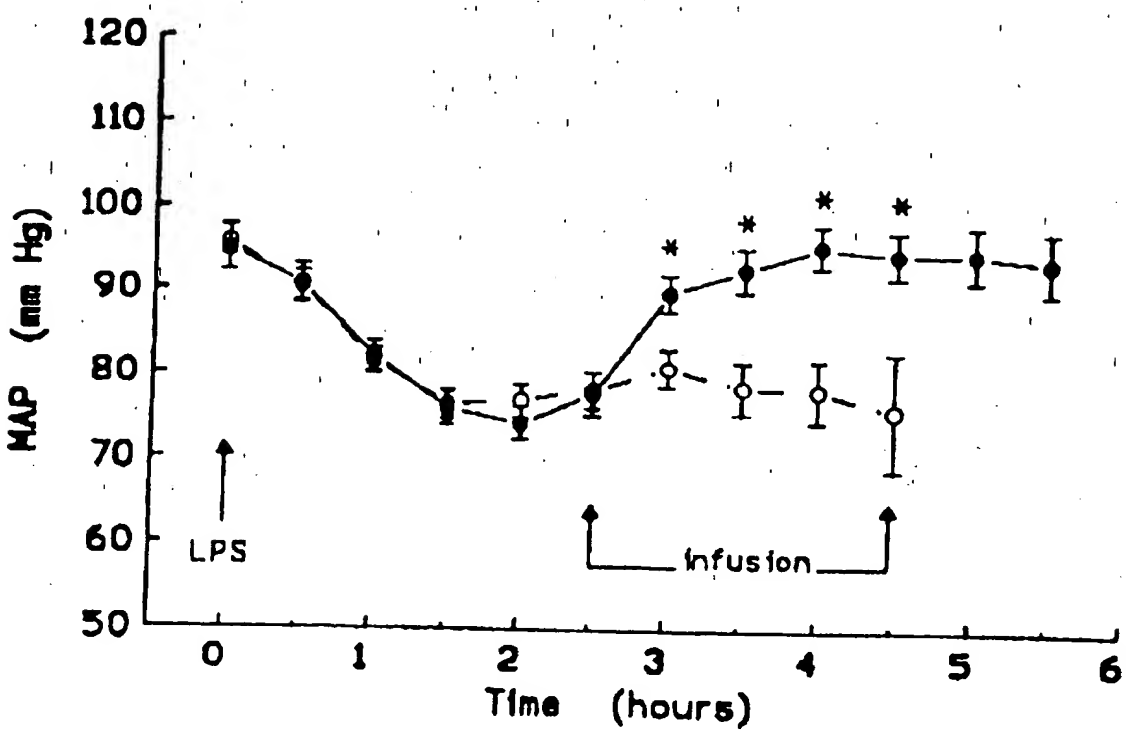
33. A composition according to claim 21 wherein said agent is selected from anti-endotoxin agents, inhibitors of cytokine synthesis/release, anti-cytokine agents, inhibitors of the coagulation cascade, inhibitors of complement activation, inhibitors of platelet activating factor, inhibitors of arachidonate metabolism, inhibitors of nitric oxide synthase enzymes, immunosuppressive agents, diabetic therapeutic agents, therapeutic agents for inflammatory diseases or therapeutic agents for Crohn's disease therapy, anti-cytokine antibodies, anti-cytokine receptor antibodies, anti-endotoxin antibodies, bradykinin antagonists, synthetic peptide blocking bradykinin receptors, bactericidal/permeability increasing protein or antibodies to platelet activating factor.

34. A composition according to claim 13 wherein said pharmaceutically acceptable carrier is selected from a solid, solution, emulsion, dispersion, micelle or liposome.

35. A composition according to claim 13 wherein said composition further comprises an enteric coating.

36. A composition according to claim 13 wherein said therapeutic agent for ophthalmic disease is a topical corticosteroid, an immunosuppressive agent, an antibiotic, azathioprine, ceftriaxone, drop preparations, artificial tears, topical lodoxamide, acetazolamide, pilocarpine, timolal, levobunolal, metipranolol, ganciclovir, fascarnet, methylprednisolone, prednisolone, cyclopentolate, salicylate, indomethacin, phenybutazone or dexamethazone.

FIGURE 1



INTERNATIONAL SEARCH REPORT

Internatio. al application No.
PCT/US96/18124

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : A61K 31/325
US CL : 514/491

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/491

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic da.a base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,358,703 A (LAI) 25 October 1994 (25.10.94), see especially column 3, lines 48-56.	1-33
Y	EIZIRIK et al. Cytokines Suppress Human Islet Function Irrespective of Their Effects on Nitric Oxide Generation. J. Clin. Invest. May 1994, Vol. 93, pages 1968-1974, especially the abstract.	1-33
Y	HAMID et al. Induction of Nitric Oxide Synthase in Asthma. The Lancet. December 1993, Vol. 342, pages 1510-1513, especially page 1510, right hand column.	1-33

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search
16 JANUARY 1997

Date of mailing of the international search report
25 FEB 1997

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231
Facsimile N . (703) 305-3230

Authorized officer
LYMAN SMITH
Telephone N . (703) 308-1235

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/18124

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	VON RITTER et al. Gastric Mucosal Lesions are Induced by Hemorrhagic Shock in Baboons. Role of Oxygen-derived Free Radicals. Digestive Diseases and Sciences. 1988, Vol.33, No.7, pages 857-864, especially the abstract.	1-33